Interactions between drug effects and environments II

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[The Table of Contents can be updated by going to the "References" menu in the toolbar, then "Update Table".]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

[Add frequently used abbreviations here. Delete any abbreviations that are not applicable to your research.]

COI	Conflict of Interest
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
FERPA	Family Educational Rights and Privacy Act
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBC	Institutional Biosafety Committee
ICD	Informed Consent Document
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IDS	Investigational Drug Service
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Authorized Representative
OHRP	Office of Human Research Protections
OPRS	Office for the Protection of Research Subjects
PHI	Protected Health Information
PI	Principal Investigator
PPRA	Protection of Pupil Rights Amendment
QA/QI	Quality Assurance/Quality Improvement
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

1.0 Project Summary/Abstract

Learned associations between a drug and the people, places and paraphernalia (cues) linked with drug experiences are considered critically important in the development of addiction by some of the leading researchers in the addiction field. These associations, formed through the process of drug conditioning, are robust and long-lasting, inducing drug craving and relapse long after the user has become drug-free. However, few studies have examined the conditioning process in humans and little is known about how the associations are formed and their influence upon behavior and drug use. The goal of the proposed research is to provide an understanding of how conditioned associations between methamphetamine, a prototypical stimulant drug, and distinct contexts are formed and how the associations influence behavior, mood and responses to the drug using a de novo conditioning model in recreational drug users. This novel model, developed by the PI, is particularly well-suited for studying conditioned drug associations because exposure to drugs and drug-paired contexts can be carefully controlled allowing a comprehensive analysis of the data. Our working hypothesis is that methamphetamine-paired environments will induce approach behavior and also alter acute subjective responses to d-methamphetamine. The rationale for the project is that vital knowledge regarding conditioned behavioral responses (e.g., impaired behavioral control) in conditioned drug contexts and may lead to novel strategies to counteract their influence on drug consumption. Moreover, a better understanding of how conditioned contexts influence behavior may inform current cue exposure therapy techniques which often do not translate to multidimensional drug associated contexts. The hypothesis, based upon strong pilot data collected by the PI, will be tested by three specific aims:

1) To determine the influence of methamphetamine place conditioning upon time spent in the drug-paired context
2) To determine the relationship between individual differences in methamphetamine place conditioning and (i) acute responses to the drug, (ii) demographic characteristics
3) To determine context-dependent responses to methamphetamine challenge following place conditioning with methamphetamine.

The proposed research is innovative because it applies well-established pre-clinical methodology to the study of drug conditioning processes in humans. The project is significant because it will provide the first evidence of direct links between psychostimulant conditioning and drug taking, and insight to the underlying behavioral mechanisms.

2.0 Background/Scientific Rationale

Learned associations between a drug and the people, places and paraphernalia (cues) linked with drug experiences are considered critically important in the development of addiction by some of the leading researchers in the addiction field [1-5]. These associations, formed through the process of drug conditioning, are robust and long-lasting, inducing drug craving and relapse long after the user has become drug-free [6, 7]. However, few studies have examined the conditioning process in humans and little is known about how the associations are formed and their influence upon behavior and drug use. Thus, there are few strategies to specifically address these pathological associations in the treatment of drug addiction. One behavioral approach aimed at dampening responses to conditioned drug cues is exposure therapy. This method consists of repeated presentations of the cue in the absence of the drug, which results in a gradual reduction of conditioned responses through Pavlovian extinction learning [8]. This approach has been shown to work well in animal models however its efficacy has been rather less convincing in the human clinic [9]. Therefore, responses to conditioned cues remain a significant barrier to the effective treatment of drug addiction. An understanding of how conditioned associations between drugs and contexts are formed and their influence on behavior will help us to design novel approaches to counteract their powerful influences.

Recently, we have developed a model to establish conditioned associations between drugs and environments in human volunteers [10, 11]. In our first studies, repeated pairings between *d*-methamphetamine and a distinct environment induced a subjective preference for the methamphetamine-associated environment over one associated with placebo. We also reported that administration of methamphetamine in a consistent produced sensitization to the drug's psychostimulant and incentive motivational effects. In more recent pilot studies with alcohol, we have developed a behavioral measure of conditioning; individuals spend significantly more time in an alcohol-paired environment than one paired with control drinks during a test of preference. We also found that individuals reported less negative subjective effects after a challenge alcohol drink in the alcohol-paired environment than in the one paired with control drinks. Finally, and most notably, individuals consumed more alcohol in the alcohol-paired environment than the one paired with control drinks. These findings demonstrate for the first time that previously neutral stimuli (contexts) paired with drugs can directly influence drug effects and drug consumption. Now we aim to build upon these promising pilot data and extend our findings with methamphetamine. We will determine the influence of methamphetamine place conditioning upon drug seeking (approach to and time spent in the drug-paired place), mood and acute responses to methamphetamine. We will also determine how individual differences in *d*-methamphetamine place conditioning are related to acute responses to the drug and demographic characteristics.

3.0 Objectives/Aims

The goal of the proposed research is to provide an understanding of how conditioned associations between methamphetamine, a prototypical stimulant drug, and distinct contexts are

formed and how the associations influence behavior, mood and responses to the drug in recreational drug users.

Aim 1a: To determine the influence of methamphetamine place conditioning upon time spent in the drug-paired context. We hypothesize that individuals will spend significantly more time in a context paired with methamphetamine at test than at the start of the experiment.

Aim 1b: To determine the relationship between individual differences in methamphetamine place conditioning and (i) acute responses to the drug, (ii) demographic characteristics. We hypothesize that individuals who exhibit greater sensitivity to the acute positive subjective effects of methamphetamine will exhibit the largest increases in time spent in the drug-paired context at test.

Aim 2: To determine context-dependent responses to methamphetamine challenge following place conditioning with methamphetamine. We hypothesize that (i) methamphetamine will produce greater subjective stimulation among subjects tested in the drug-paired room than those tested in the placebo-paired room.

4.0 Eligibility

Healthy men and women (N=150 total) will be recruited provided they meet the screening criteria; age 18-40, body mass index 19-26kgm-2 (previous studies in this laboratory indicate that responses to 20mg methamphetamine do not vary within this range), at least a high school education, fluency in English and a normal ECG. Exclusionary criteria are; history of a Major Axis I disorder [12], serious medical condition, history of cardiac disease, high blood pressure, history of drug or alcohol dependence (determined in the diagnostic interview), >4 alcoholic or caffeinated beverages a day, or night shift work. Subjects must report some prior recreational use of illicit drugs (incl. amphetamines) for both safety reasons (participants who report previous adverse reactions can be excluded) and data validity reasons (subjects should be able to accurately describe drug subjective effects). Subjects will be randomly assigned to 4 groups; Paired groups 1-3 (N=40 each) and an Unpaired group (N=30). The groups will be matched for prior stimulant use and sex.

Eligibility is determined during a screening process that is approved under IRB protocol 2014-1060. The criteria for the different studies that are conducted in our laboratory vary only slightly from study to study, and often subjects are screened for one study, yet qualify for another. Therefore, we find it is more cost-effective and time-efficient to conduct a general laboratory screening procedure after which subjects may be enrolled into one of a number of studies. The screening procedure is described in detail below.

4.1 Inclusion Criteria

- Age 18-40
- Body mass index 19-26kgm-2

- At least a high school education
- Fluency in English
- Normal ECG
- Subjects must report some prior recreational use of illicit drugs (incl. amphetamines)

4.2 Exclusion Criteria

- History of a Major Axis I disorder [12]
- Serious medical condition
- History of cardiac disease
- High blood pressure
- History of drug or alcohol dependence
- >4 caffeinated beverages a day
- Night shift work
- Abnormal ECG
- Abnormal menstrual cycle
- >5 cigarettes/day
- Participants who report previous adverse behavioral or physiological reaction to amphetamines
- Positive personal or family history of liver disease
- Positive personal or family history of glaucoma
- Positive personal or family history of hyperthyroidism
- Obesity (body mass index outside of 19-26kgm-2
- Diabetes mellitus (types 1 and 2)
- Hyperlipidemia
- Males consuming >3 units of alcohol per day and females consuming >2 units of alcohol per day
- Positive test for Hepatitis B and C
- Past month use of antibiotic medications
- Right upper quadrant pain
- Changes in appetite, or weight loss without appetite change
- Persistent eye pain or recent change in vision

4.3 Excluded or Vulnerable Populations

- Women who are pregnant, lactating or planning to become pregnant will be excluded because the study involves alcohol administration which is harmful to the foetus.
- Subjects who are not fluent in English or who have not completed high school will be excluded because these are the minimum requirements to be able to complete the study questionnaires.

5.0 Subject Enrollment

Recruitment and screening procedures are conducted under protocol #2014-1060. Subjects are recruited using approved flyers posted in the local community and on-line (e.g., Craigslist) or newspaper advertisements. These flyers and adverts detail a range of ages and eligibility criteria for the studies being conducted in our lab

Subjects respond to adverts to indicate their interest in participating in the studies and then complete a brief online survey or telephone interview with the research staff to determine initial eligibility. If they meet the initial eligibility criteria (age, lack of medications, previous drug use history), they are then invited to the laboratory for an in-person screening interview..

At the screening visit, potential subjects undergo a structured clinical psychiatric interview with trained research staff (to exclude persons with psychiatric disorders including substance dependence, APA 2013). Information is also obtained on current and recent history of medical problems (to exclude individuals with contraindicated conditions such as cardiac disease) and current and recent drug use history (to exclude individuals with substance dependence). They also complete standardized questionnaires including a psychiatric symptom checklist (35), the Beck Depression Inventory (36) and the Michigan Alcoholism Screening Test (37). Past month drinking is assessed using the standardized Timeline Follow-back (38) interview. An EKG is also obtained by the trained research staff, which is reviewed by the study physician, Dr. Nathan, for abnormalities.

Once the screening procedures are complete the researcher reviews the information to provide a preliminary determination of eligibility based on study criteria. Eligible subjects are told that the final determination for eligibility lies with the study physician. The study design and procedures are then described in detail to eligible participants to determine their interest in participating. They are also informed that the study will not directly benefit them. If they decide to participate in the study, an orientation visit is scheduled (see below).

6.0 Study Design and Procedures

The study will be conducted at the Human Behavioral Pharmacology Laboratory at the Psychiatric Institute at UIC. Study sessions will be conducted using two testing rooms, which are similar in size and furnished as comfortable living areas; each has a window, a couch, an easy chair, a side table, a coffee table and bookcase with reading material, a television and video player, a desk with a computer, and pictures on the walls. The rooms are distinct in terms of the color of the couches, cushions, accent furnishings, pictures on the walls and scents. Cameras mounted in the upper corner of each room record subjects' movements during the room choice tests. When subjects are not completing study procedures they may relax, read or watch television.

The study involves seven separate visits to the laboratory. The first visit is an orientation session at which subjects are enrolled into the study. Visits 2-5 are drug administration

sessions. Visit 6 is a testing session that will also involve drug administration. Visit 7 is a debriefing session.

Visit 1 - Orientation Session: Subjects will read and sign the study consent form which states that the study aims to investigate interactions between drug effects and the environment. The consent form lists classes of drugs i.e., stimulant, sedative, alcohol, or placebo, they might receive and possible side effects. Subjects are not informed about the drug that they will receive ahead of the study to avoid effects of expectancy upon the study measures (see Appendix J). Subjects are fully debriefed about the drugs received at the end of the study at the debriefing session. Other drugs are listed to prevent expectancy effects. Subjects are informed that they should not schedule any activities for periods immediately following the experimental sessions because they may receive an active study drug that may influence their ability to perform these activities. On the consent form, subjects are informed that they must not drive following study sessions (compensation for public travel will be provided if necessary), or use any recreational drugs except for their normal amounts of caffeine for 24h before and 6h following each session, and not to operate any machinery requiring concentration for 6h following the sessions because this may be hazardous to their safety. By signing the consent form, subjects indicate that they will comply with these conditions. Subjects may consume their usual amounts of caffeine before sessions to prevent the possibility of caffeine withdrawal. We do not expect that small doses of caffeine will interact with methamphetamine or affect the outcome measures. Subjects also complete a behavioral Room Preference test (see 'Dependent Measures' section) to assess baseline room preference. They will also practice the tasks and questionnaires to be administered during later sessions so that they are familiar with the study procedures. Some tasks may have additional small monetary rewards for good performance (up to $10) that is paid in cash at the end of the orientation session (see Behavioral Tasks, page). Subjects will provide a saliva sample for genotyping (Oragene, DNA Genotek) and a blood sample (50mL) for analysis of biological correlates (see details on page 12 regarding saliva and blood specimens). Blood draws will be performed at the Human Addiction Psychopharmacology Laboratory by a trained professional.

Visits 2-5 – Drug administration Sessions: These sessions begin at 9am and are conducted at least 2 but not more than 7 days apart. Women, who are not using hormonal birth control, will be randomly assigned to participate in the follicular (days 1-10) or luteal (days 5-25) phase of their menstrual cycle. Women assigned to the follicular phase, will call the Research Assistant on day 1 of their cycle to schedule their sessions. Women assigned to the luteal phase will be given ovulation test kits (urine dip sticks) to test their urine on days 10-15 of their cycle. When they receive a positive test (which indicates that ovulation is about to occur), they will call the researchers to schedule their sessions. On arrival, subjects will provide breath and urine samples to detect recent alcohol and drug use, and pregnancy in women. The session will be cancelled if any of the tests are positive. Subjects will be escorted to the testing room for that session depending on the treatment (drug or placebo) that they are to receive. To maintain the double-blind conditions, the PI (Dr Childs) will determine the drug and placebo session order (counterbalanced between individuals) and assign the drug and placebo rooms for subjects in the Paired Group based on their pre-existing preferences. Paired Group subjects will receive methamphetamine and placebo on alternating sessions i.e., A, P, A, P etc. or P, A, P, A etc.

Subjects will relax in the room for 15 min before baseline measures are collected. At 9:30am, they will consume a capsule that contains 20mg methamphetamine or placebo. They will complete standardized subjective effects questionnaires (to measure drug effects) and vital signs will be collected every 30 min after capsule administration until 11:30am (to allow peak drug effects to be experienced, approx. 60 min after administration of capsules). At the end, subjects rate their overall experiences. See safety guidelines (page 16) regarding release of subjects after drug administration.

Visit 6 - Testing Session: This session will begin at 9am and is conducted at least 2 but not more than 7 days after the last drug administration session. On arrival, subjects will provide breath and urine samples to detect recent alcohol and drug use, and pregnancy in women. The session will be cancelled if any of the tests are positive. Subjects first complete a Room Preference Test (see 'Dependent Measures' section) to measure time spent in the testing rooms. Subjects will then undergo a drug challenge test in one of the testing rooms; Paired Group 1 (PG1) will receive 20mg methamphetamine in the drug-paired room, PG2 will receive 20mg methamphetamine in the placebo-paired room, and PG3 will receive placebo in the drug-paired room (NB: although we have not formulated specific hypotheses regarding PG3, this group will allow us to dissociate the contribution of expectancy and pharmacological effects to the responses exhibited by PG1). Unpaired group subjects will be randomly assigned to receive methamphetamine or placebo in one of the testing rooms. After relaxing in the designated room for 30 min, baseline measures will be collected. Subjects will then consume the capsule. Subjective measures and vital signs will be obtained every 30min (at 30, 60, 90, and 120min). At the end, subjects rate their overall experiences (see safety guidelines on page 16 for information regarding release of subjects after drug administration).

Visit 7 - Debriefing and Payment: Subjects will attend a short interview with the senior investigator one week after their final testing session at which they are fully debriefed about the study aims, the drug received and may ask questions. They are paid $250 in cash for completing all study requirements. Subjects who drop out of the study early will be paid for the number of sessions completed based on the payment schedule below. This information is conveyed to subjects at the orientation session verbally and in the consent form.

The table below details each of the visits, the length of each visit, and the procedures that will be performed at each session during the study. The payment structure is also shown. Please note that payments are not made at each session, but are made in check form at the debriefing session as stated above.

Table 1: Study visits and procedures

Visit	Session and length	Procedures	Payment
1	Orientation 1h	Sign consent form, practice study questionnaires, collect saliva and blood samples. Transportation not provided.	Up to $10 (for task performance)[1] $10*

2	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure heart rate, blood pressure.	$30*
3	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure heart rate, blood pressure.	$30*
4	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure heart rate, blood pressure.	$30*
5	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure heart rate, blood pressure.	$30*
6	Testing session (with drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete tasks, mood questionnaires and measure heart rate, blood pressure.	$30*
7	Debriefing session 30-60 min	Debriefing about study aims. Payment* Transportation not provided.	$90*
		TOTAL FOR STUDY VISITS	**$250***

[1]Payments for task performance are paid in cash at the end of the orientation session.
*Payments for completing each session will be made at the debriefing session in cash.

Behavioral Tasks: The *Delay Discounting Task* measures impulsive choice by assessing the relative value of immediate versus delayed rewards. This task has been used extensively in drug abuse research, and studies have consistently shown greater discounting of delayed rewards by substance abusers. Subjects complete this task at the orientation session. In the task, participants make a series of choices (90 total) between a smaller amount of money (ranging from $0.50 to $10) available immediately, and a larger amount of money ($10) available after a delay (i.e., 1, 2, 7, 14, 30, 60, 90, 180, or 365 days). They are told that at the end of the task, one of the questions will be selected at random and that they would receive whatever they answered to that question. Thus, subjects perform the task knowing that they will receive one of their choices (money now or later). This condition has been shown to enhance attention to the task and the accuracy of responding. In actuality, the research assistant checks the database to find a question to which the participant answered '$8-10 right now' and they are given $10. The $10 for task performance is separate to the $10 that subjects receive as compensation for completion of the orientation session.

Dependent Measures: *1. Room preference* will be assessed during a 10min Room Preference Test during which subjects are instructed to explore the testing rooms and to spend as much time as they like in each room. They are asked to pay particular attention to details such as scents, temperature, lighting, décor, and furniture. Camcorders placed in each room record participants' movements during the preference test and the amount of time spent in each room

is calculated (% of total time). *2. Subjective mood and drug responses* will be assessed using standardized questionnaires;

- The Addiction Centre Research Inventory, ARCI. This is a true–false questionnaire that consists of empirically derived scales sensitive to the effects of a variety of classes of psychoactive drugs (Haertzen 1966). We use 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)].
- The Drug Effects Questionnaire, DEQ. This consists of five 100-mm horizontal lines each labeled with a question; “Do you feel any drug effect?” (rated from “none at all” to “a lot”), “Do you like the effects you are feeling now?” (rated from “not at all” to “like very much”), “Do you dislike the effects you are feeling now?” (rated from “not at all” to “dislike very much”), “Are you high?” (rated from “not at all” to “very”), and “Would you like more of what you consumed, right now?” (rated from “not at all” to “very much”).
- The Profile of Mood States, POMS. This is a 72-item adjective checklist on which subjects report their current mood on a 5-point scale from “not at all” (0) to “extremely” (4). Eight clusters (scales) of items are separated empirically by factor analysis (anxiety, depression, anger, vigor, fatigue, confusion, friendliness, elation). Two summary scales are derived from the other scales as follows: arousal = (anxiety + vigor)–(fatigue + confusion); positive mood = elation–depression.

Subjects also complete an End of Session Questionnaire (ESQ) at the end of each session to rate their overall experience and to indicate what drug they think they received. Vital signs will be measured at repeated intervals.

For Specimen Collection Studies

1) *Saliva Samples:* DNA for genetic analysis will be extracted from saliva samples collected during the orientation session. Saliva samples will be stored in a locked cabinet in the PI’s laboratory until analysis is performed. Samples will be coded and the file linking subjects’ names and IDs will be kept in a separate secure location in the PI’s office. Once extracted, coded DNA samples (from saliva) will be stored in a locked freezer in the PI’s laboratory and kept for a period of 6 years following the study. Genetic analyses will identify potential genetic factors that influence responses to stimulant drugs and the development of environmental conditioning. These analyses will focus upon associations between genetic variants in, for example, drug receptor genes and the outcome measures i.e., time spent in the drug-paired room, subjectively rewarding effects of methamphetamine. For example, these analyses may include analysis of single nucleotide polymorphisms (SNPs) in the dopamine transporter gene. Genetic samples will be collected over the course of the study and stored in a locked cabinet in the PI’s lab for batch analysis at the end of the study.

2) *Blood samples:* RNA DNA, genes levels and plasma proteins will be extracted from the blood samples (50mL) collected at orientation. Samples will be processed immediately for analysis of biological correlates. 20mL will be dedicated to the isolation of lymphocytes, 20 mL to gene expression studies and 10 mL for evaluating plasma protein.
**The rationale for collection of blood samples for analysis of biological correlates is that drug use can induce changes in gene function that occur without a change in the body's genetic code. We will collect lymphocytes and proteins present in blood samples in order to look at gene function in these recreational drug users. These analyses will include genes and markers for BDNF, CRF, NPY among others. This pilot data will be used to form a later grant application to the NIH.

Behavioral Intervention Studies

Videotapes of subjects' movements during the room preference test will be stored on a password-protected computer in the PI's laboratory. Videos will be destroyed after the data is published.

Survey studies

All questionnaires are standardized and are widely used in human laboratory studies to measure drug effects.

Studies involving use of product

Methamphetamine tablets (Mallinckrodt Pharmaceuticals, MI) will be obtained from the Hospital Pharmacy and will be administered in opaque gelatin capsules with dextrose filler. Four 5mg methamphetamine tablets will be placed into one single capsule. Placebo capsules will contain only dextrose filler. Individuals are given a glass of water with which to consume the capsules.

7.0 Expected Risks/Benefits

The risks to subjects involve risks of 1) confidentiality, 2) administration of methamphetamine, 3) completion of questionnaires, and 4) blood draws. The possible adverse effects of methamphetamine include:

- constipation
- memory loss
- dizziness or faintness
- restlessness
- double or blurred vision
- shakiness or tremor
- coordination problems
- changes in sex drive
- rapid heart rate
- dryness of the mouth
- raised blood pressure
- nausea or muscle weakness
- drowsiness
- depression
- confusion
- tiredness
- slurred speech
- headache

These reactions are unlikely at the dose administered in this study, and in these healthy volunteers. In addition, subjects must report prior recreational use of illicit drugs including amphetamines, without adverse effects. We have previously administered 20mg methamphetamine in our laboratory with few, if any, adverse effects. In order to minimize risks to subjects, we will only enroll individuals who report previous recreational drug use including alcohol, tobacco or marijuana use. The large majority of occasional psychoactive drug users do not go on to use them excessively and there is no evidence that participating in controlled laboratory studies such as these increases the risk for developing substance use problems [18-21].

Some risks are associated with the blood draw. These include bruising and pain at the site of needle insertion, and a small risk for infection. Samples will be drawn by a certified phlebotomist who is trained in methods of reducing risks. In addition, standard sterilization techniques will be utilized in order to minimize the risk of needle-site infections.

Potential benefits of the proposed research to subjects and others: subjects will benefit from the information obtained during the screening procedure (e.g., physical examination and electrocardiogram, as well as psychiatric screening). This is particularly beneficial to individuals who are excluded during the screening because of some previously undiagnosed condition. These individuals are referred for treatment. Subjects are paid for their participation. They may also request information about their performance and responses during the studies.

Importance of the knowledge to be gained: the risks to subjects are justified by the knowledge to be gained. The findings will further our understanding of an important yet understudied clinical issue in a controlled manner, that is, how psychoactive substances come to powerfully control mood and behavior which is central to the development of drug addiction. The project will important to the wider addiction research community, both basic science and clinical. The findings will be important from a basic science and also a clinical perspective. This human model has a clear parallel in preclinical research and provides a critical translational link to preclinical data. An understanding of how contextual conditioning is established with the prototypical stimulant drug methamphetamine can be applied to the processes of contextual conditioning of other drugs. The findings and model can be used to design future investigations into methods to disrupt contextual conditioning and its consequences, particularly conditioned drug craving. Ultimately the data will inform existing treatment practices e.g. exposure therapy, and aid development of new approaches to curb drug use. Thus, new methods that break contextual associations or which counteract their influence on mood and behavior will improve current strategies to help achieve and maintain drug abstinence.

8.0 Data Collection and Management Procedures

Subjective data will be collected using standardized paper forms and computerized questionnaires. Each subject will be given a unique code. The data will only be identified with the subject's ID for that study. The PI will keep the codes that link the name of the participant

and the study ID in a secured cabinet. Data from paper forms will be entered in the computer by trained staff, and discrepancies corrected by a supervisor based on source documents. Computerized tasks will be administered using ACCESS and stored in a database on password protected computers in the PI's laboratory.

9.0 Data Analysis

The primary measures are (i) change in % time spent in the drug-paired room, (ii) ratings of subjective stimulation (ARCI) during conditioning, and (iii) ratings of subjective stimulation during the re-exposure test session. Sample size calculations are presented in table 1 (below).

Aim 1a: To determine the influence of methamphetamine place conditioning upon time spent in the drug-paired context. *We hypothesize that the paired group will spend significantly more time in a context paired with methamphetamine at test than the unpaired group.* We will compare the change in time spent in the initially less-preferred room between the paired and unpaired groups using t-tests.

Aim 1b: To determine the relationship between individual differences in methamphetamine place conditioning and (i) acute responses to the drug, (ii) demographic characteristics. *We hypothesize that individuals who exhibit greater sensitivity to the acute positive subjective effects of methamphetamine will exhibit the largest increases in time spent in the drug-paired context at test.* We will examine the association between methamphetamine subjective responses (stimulation and drug liking) after the first administration and the change in time spent in the drug-paired room at test using correlation analysis. Power calculations based on an N of 90, with 80% power and a significance level of $p<0.05$ (2-sided) indicate that we will be able to detect a significant association if the true correlation coefficient is 0.3 (a medium effect size). In exploratory analyses we will investigate differences in demographic, personality and drug use characteristics between paired group subjects who acquire conditioning (≥10% increase in time spent in drug-paired room) in comparison to those who do not (no change or a decrease in time spent in drug-paired room) using independent sample t-tests. Pilot data from our studies indicates that approximately 30% of subjects do not acquire conditioning.

Aim 2: To determine context-dependent responses to methamphetamine and placebo challenge following place conditioning with methamphetamine. *We hypothesize that methamphetamine will produce greater subjective stimulation among subjects tested in the drug-paired room than those tested in the placebo-paired room.* We will compare subjective stimulation after 20mg methamphetamine between paired group subjects tested in the drug-paired and placebo-paired rooms using independent samples *t*-test.

Table 2: Calculations of [1]required sample size to detect observed effects (2 sided test, α=0.05, power=80%) and [2]the probability to detect significant differences for the specific aims. Calculations were based upon preliminary data (section C1.4). *indicates a within-subjects *t*-

test. [#]indicates a between-subjects *t*-test. [¥]Sample sizes are lower than the number enrolled in each group as we expect 70% of subjects in the paired groups to acquire conditioning (Fig 3b).

Aim	Outcome Measure	N[¥]	SD	Difference	N[1]	Power[2]
1a	Change in % time spent in drug-paired room*	60	22.7	12.4	30	98
	Change in % time spent in drug-paired room[#]	80	20.0	13.7	70	85
2	Stimulation[a] (ARCI A)[#]	40	11.0	13.0	26	95

10.0 Quality Control and Quality Assurance

The PI is responsible for adherence with the protocol and accuracy in data entry. All data will be double entered and checked for accuracy. The PI will meet with research staff on a weekly basis to review procedures and data collection, and to troubleshoot any unanticipated problems. Data will be analysed after every 10 subjects enrolled to check on the effect size.

11.0 Data and Safety Monitoring

The study involves a non-vulnerable population. Therefore, the PI and study physician will monitor the study for safety and adherence to the protocol. The PI and Dr. Nathan will approve each subject before he or she begins any study procedures to ensure that only subjects who meet the eligibility criteria are enrolled. The PI will also review the informed consent of every subject, supervise data collection and analysis, and ensure that privacy and confidentiality are maintained as described in this document.

During the study sessions, vital signs (heart rate and blood pressure) are monitored at 30-minute intervals and there are guidelines to follow regarding overt changes in these vital signs (see below).

Determination of AEs: Adverse events are defined as any incidence when the PI or Dr. Nathan is consulted regarding participant vital signs or side effects. Any side effects reported in the medium to severe range will be classified as an adverse event. Data and safety monitoring will be performed by the PI. Each month a report will be compiled that lists the number and details of adverse events (see Appendix) which will be discussed with the study physician.

Possible adverse events (AEs) include:

- Excessive increases in heart rate and blood pressure.
- Side effects of methamphetamine that cause significant impairment.

During each session, heart rate and blood pressure are monitored before drug administration and at 30 min intervals following drug administration. Subjects also report any side effects that they may be feeling using a paper and pen questionnaire. The following is a set of guidelines developed with the study physician regarding monitoring of vital signs and side effects during sessions.

Safety and Monitoring Guide

Baseline measurements i.e., before drug administration:

Heart rate and blood pressure must within the "normal" range in order for the session to go ahead. Remember that subjects have often travelled on public transportation and may have rushed to the session to be here on time, so it is best to have them rest for at least 20 min before baseline measurements are obtained. In addition, heart rate and blood pressure tend to decline across the testing session while subjects are sedentary.

Systolic	Diastolic	Heart rate	What To Do:
< 140	< 90	< 99	These values are within the "normal" range; proceed with other measures and drug administration
>=140	>=90	>=99-119	This is higher than "normal"; have the subject rest quietly and take another reading 10 minutes later. If reading is still above the "normal" range, rest and repeat once more 10 min later. If participant's readings do not come down to the normal range, see instructions below.

What to do if the subject has a reading in the "higher than we want" range, and it won't come down after a few readings:

- **Look in their subject folder for the vitals taken at their screening.** Contrast this reading with your current one; how different are they? If they're very different, the questions below may explain it. Have this info ready for Dr. Childs/Dr Nathan.
- **Say to the subject in a casual tone,** "Your (blood pressure/heart rate) is looking a bit on the high side today. There are a lot of factors that can affect (blood pressure/heart rate), so I'd like to ask you a few questions:
  - **How much sleep did you get last night?**
  - **How much caffeine have you had in the last 12 hours?** (You should have asked this before anyway, but you can delve a bit deeper and double-check their 12-hour/current use versus their "typical" use)
  - **Are you feeling stressed out?**
  - **Did you hurry coming in here?"**
- **Record their answers on your session flowsheet.** Be thorough in your documentation.
- **Call Dr Childs** to discuss (5-2726). If you can't reach Dr. Childs, call the study physician, Dr. Nathan (6-9518).

Within-session measurements i.e., after drug administration:

These measurements are taken post-capsule administration and are expected to change throughout the session. Do not use these measurements to play guessing games about what the capsule contained. If a participant's blood pressure goes up, this is a normal drug response so do not get nervous and definitely do not make the participant nervous. Just follow the instructions in the guide in an appropriate and timely manner.

If the Systolic Reading Is…	If the Diastolic Reading Is…	If the Heart Rate Is…	What To Do:
< 140	< 90	< 99	It's in the "normal" range.
140-179	90-99	<99	Check the side effects form for any symptoms. If nothing reported, continue to monitor regularly. If any side effects are reported, casually enquire about how they are feeling. If the subject also reports headache, muscle pain, chest pain, nausea, pounding heart or subjective distress (anxiety, tension) notify Dr. Childs and call Dr. Nathan to discuss.
180 or higher	100 or higher	100 or higher	Casually ask the participant how they are feeling. **If they report no other symptoms,** have them sit quietly for 10min. Take another reading and if it is still in this range, contact Dr. Nathan for assistance (even if they say they feel fine). **If they report** headache, chest pain, nausea, pounding heart or subjective distress (anxiety, tension), contact Dr. Nathan for assistance right away (don't wait for a second reading).

End-of-session measurements

Vital signs must be within 20% of the baseline measurements in order to discharge the subject. If vitals are above these values, continue to monitor every 15min. Subjects who report any side effects in the medium range may require assistance to travel home (i.e., taxi cab or have a friend come to get them). If any of these conditions are present at the end of the session, do not discharge the subject until you have consulted with Dr. Nathan. If all measurements are within the "normal" range (i.e., within 20% of baseline, no significant side effects), discharge the subject with a Post-session Side Effects form for them to report any unusual signs or symptoms over the next 24h.

Reporting of SAEs: Although they are unlikely, all adverse events (AEs) occurring during the course of the study will be reported to the Principal Investigator and study physician. All AEs will be followed until resolved satisfactorily. Subjects who experience AEs will be withdrawn from the study. AEs will be evaluated for SAE criteria (defined by the FDA). If an SAE should occur, it will be reported to the IRB of The University of Illinois at Chicago, NIDA, and any other appropriate agencies within 5 days of occurrence. The initial report will be followed by a complete SAE report, sent to all institutions. If a subject or the investigator discontinues the

subject's participation due to an SAE, the subject will receive follow-up medical care as necessary. Follow-up care will continue until the subject no longer requires hospitalization, the condition is stabilized with no future change expected, or the problem is determined to be unrelated to the drug used in the study. The annual progress report submitted to NIDA will contain a summary of any SAEs occurring in the previous year.

Reporting of IRB actions to NIDA: Any IRB actions on the protocol, including continuing reviews and protocol amendments, will be communicated in the annual progress report to NIDA.

Reporting protocol changes and amendments: Any protocol changes or amendments to the procedures will be communicated in the annual progress report to NIDA.

Trial stopping rules: The study will be stopped if there is an inappropriate increase in the risks to participants (assessed by the rate of AEs and SAEs) or if the effect size is deemed too small in preliminary analyses of study data.

12.0 Statistical Considerations

See earlier section 9.0 Data Analysis.

13.0 Regulatory Requirements

13.1 Informed Consent

Subjects read and sign the study consent form at the orientation session conducted at the Human Psychopharmacology Laboratory with the senior study investigator. They are told that the purpose of the study is to investigate interactions between drug effects and the environment. The study will be fully explained to the subject at several instances (e.g. first contact, at the orientation session) before subjects read and sign the consent form. All subjects will be fluent in English in order to understand the standardized study measures. There is also a waiting period of at least 2 days between signing the consent form and beginning the study such that the subject has time to fully re-review the study information and their decision to participate. All members of the research team will complete the required CITI training procedures for studies involving human subjects. The consent form will be stored in the subject's research record that is stored in a locked cabinet in the PI's laboratory.

13.2 Subject Confidentiality

Subjects are assigned a study ID that is used to identify them on all study data. The file linking IDs to subject names is kept in a separate location to the data in a locked filing cabinet in the PI's office. Only research staff who work on the study will have access to the data. Personally identifiable data is required in order to ensure eligibility for the study and to be able to contact subjects to schedule study visits.

13.3 Unanticipated Problems

The PI and study physician will monitor the study for safety and adherence to the protocol. Any adverse events that may occur are anticipated to be mild and limited to those listed in the consent form. The PI and the study physician will be notified immediately if an adverse event occurs, and the PI will report the event to the IRB. The PI and study physician will approve each subject before he or she begins any study procedures to ensure that only subjects who meet the eligibility criteria are enrolled. The PI will also review the informed consent of every subject, supervise data collection and analysis, and ensure that privacy and confidentiality are maintained as described in this document.

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APPENDICES

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University of Illinois at Chicago
Research Information and Consent for Participation in Biomedical Research
Interactions between drug effects and environments II

You are being asked to participate in a research study. Researchers are required to provide a consent form such as this one to tell you about the research, to explain that taking part is voluntary, to describe the risks and benefits of participation, and to help you to make an informed decision. You should feel free to ask the researchers any questions you may have.

Principal Investigator Name and Title:	Emma Childs PhD, Associate Professor
Department and Institution:	Department of Psychiatry, UUIC
Address and Contact Information:	1601 W Taylor Street, Chicago IL 60612, echilds@uic.edu 312-355-2726
Emergency Contact Name and Information:	Emma Childs PhD, 773-865-4576.
Sponsor:	National Institute of Health (NIH)

Why am I being asked?

You are being asked to be a subject in a research study. The purpose of this research is to examine the interactions between drug effects and the environment. The drugs used in this experiment may be taken from one or more of the following classes of drugs:

1. a stimulant e.g. caffeine, nicotine, amphetamines
2. a sedative e.g. alcohol, benzodiazepine, antihistamine
3. a placebo (an inactive substance)

You have been asked to participate in the research because you are 18-40 years old, and have indicated during the screening process that you voluntarily consume psychoactive substances e.g., caffeine, nicotine, alcohol etc., on a recreational basis.

Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future dealings with the University of Illinois at Chicago. **If you decide to participate, you are free to withdraw at any time without affecting that relationship.**

Approximately 150 subjects may be involved in this research at UIC.

What is the purpose of this research?

We are interested in studying the interactions between drug effects and the environment. Subtle variations in environmental settings, such as smells, temperature, lighting, may interact with drug effects and alter the experiences that people feel. At several points in the study we will ask you questions about whether you like the drug effects that you may be feeling, or the room that you are in.

What procedures are involved?

This research will be performed at the Human Addiction Psychopharmacology Laboratory (HAPPY Lab) located in Suite 318 of the Psychiatric Institute at the University of Illinois at Chicago. You will need to come to the study site 7 times in order to complete the study. These visits will be scheduled at the availability of yourself and the research coordinator, and will be conducted at least 2 days but no more than 1 week apart. Thus, the duration of your participation in the experiment will vary between 14 days and 7 weeks. The first visit is an orientation session lasting 1 hour, the next 4 visits (visits 2-5) are drug administration sessions that will last about 4 hours each (usually conducted between 9am and 1pm). The sixth visit is a testing session that will also involve drug administration and will last 4h. The seventh visit will be a debriefing session that will last approximately 30-60min.

At the orientation session, you will read and sign the consent form, receive instructions about recreational drug use before the sessions, and complete behavioral tasks, computer-based tasks and questionnaires so that you are familiar with the procedures. The research assistant will also collect a saliva sample for DNA analysis and a blood sample for epigenetic analysis (see below).

The 4 drug administration sessions and the testing session will be conducted beginning in the morning at the HAPPY lab at least 2 but not more than 7 days apart. If you are a women not using hormonal birth control, you will begin your first session either during days 1-10 (follicular phase) or during days 15-25 (luteal phase) of your menstrual cycle. The researcher will randomly determine (like the flip of a coin) whether you are assigned to the follicular or luteal phase. If you are assigned to the follicular phase, you will call the researchers on day 1 of your cycle to schedule your sessions. If you are assigned to the luteal phase, you will be given ovulation test kits (urine dip sticks) to test your urine on days 10-15 of your cycle. When you get a positive test (which indicates that ovulation is about to occur), you will call the researchers to schedule your sessions. Each session will involve administration of capsules that may or may not contain an active drug and will last for 4 hours. **You must not use any drugs (including alcohol), except for prescribed medications (that have been approved by the study doctor) and your normal amounts of caffeine, for twenty-four (24) hours before any of the sessions.** In addition, you should not use other drugs for 6 hours following the experimental sessions as this may be hazardous to your health and safety. If you are taking prescribed medication, you should inform the experimenter before the experimental session. You should not drive to the study visits and should plan on a different method of transportation. You should not drive or operate complex machinery for 6 hours after the experimental sessions. You should not schedule any activities for immediately following sessions because of the possibility of drug administration during sessions. While you are participating in the experimental phase (not the follow-up) of this study you must obtain the permission of the experimenter before participating in any other research study.

Upon arrival at the laboratory, you will provide breath and urine samples to detect recent alcohol and drug use, and in women, pregnancy. If you test positive for alcohol or drug use, or pregnancy in women, your session will be cancelled and you may be withdrawn from the study. Fifteen minutes after arrival, you will complete mood questionnaires and your blood pressure will be measured. During study sessions 1-5, you will be given a capsule that could contain an active drug listed on the front of this form. Dr. Childs will randomly, like the flip of a coin, determine whether you receive an active drug or not. At various times after taking the capsule (30, 60, 90 and 120 min) you will complete mood questionnaires and your blood pressure will be

measured. During the sessions when you are not completing study measures, you may relax in the testing room by yourself and watch television, movies or read.

In this study, we are interested in studying the interactions between drug effects and the environment. Therefore, we ask you to pay attention to the environment you're in during the study sessions, and also any drug effects you are experiencing. At several points in the study we will ask you questions about whether you like the drug effects, or the room that you are in. At the end of the experimental session, you will rate your overall experience and you will be allowed to leave. As part of our laboratory procedure, some of the sessions that you participate in will be videotaped. The recordings will only be viewed by the experimenters and will be destroyed after the study.

Once all of the study procedures are completed, you will attend the laboratory one week after your final testing session for a debriefing visit at which, you will be fully informed about the drugs you received and the aims of the study (i.e., the analysis that will be performed with the data collected). You may ask questions about the study and provide feedback about your experiences. At this visit you will also be paid (up to $250) in cash. If you drop out of the study before completing all of the requirements, you will receive a cash payment for the number of sessions completed according to the payment structure shown in the table below.

The table on the next page details each of the visits, the length of each visit, and the procedures that will be performed at each session during the study. The payment structure is also shown. Please note that payments for each study visit are not made at each session, but are made in cash at the debriefing session as stated above.

During this study, Dr. Childs and her research team will collect information about you for the purposes of this research. The information we collect regarding your current and recent drug use history will be used for research purposes only, and will remain locked in our laboratory at all times. Physiological (heart rate, blood pressure), subjective (mood questions) and behavioral (computer task) data will not be labeled with your name or other identifying information. These data may be published, but will not identify you personally.

Genetic Testing

We will extract your DNA from the saliva and blood samples. DNA is the biochemical code that contains your genes, which you inherit from your parents. Genes help determine some of our individual characteristics, such as eye color, height and skin tone. Genes may also determine why people are affected by drugs and how these drugs affect them. For example, people may differ in their sensitivity to the effects of drugs because of their genetic make-up and in turn this could influence their susceptibility to use drugs. We will assess the genes that may influence your responses to the drugs administered during this study. We will also study biological mechanisms that switch genes on and off (epigenetics). A special code will be used to label your DNA, so that it can be analyzed in this study but no one else will be able to identify that it belongs to you. The Investigator will keep the name associated with each code in a locked file. This information will not be shared with you, nor will it be shared with others who are not directly related to this research study.

Table 1: Study visits and procedures

Visit	Session and length	Procedures	Payment
1	Orientation 1h	Sign consent form, practice study questionnaires, computerized tasks, collect saliva and blood samples.	Up to $10 (for tasks)[1] $10*
2	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure heart rate (HR) and blood pressure (BP).	$30*
3	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure HR and BP.	$30*
4	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure HR and BP.	$30*
5	Drug administration 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete mood questionnaires and measure HR and BP.	$30*
6	Testing session (with drug administration) 4h	Drug and pregnancy tests. Consume capsule that may contain active drug. Complete tasks, mood questionnaires and measure HR and BP.	$30*
7	Debriefing session 30-60 min	Debriefing about study aims. Payment*.	$90*
		TOTAL FOR STUDY VISITS	**$250***

[1]Payment for task performance is paid at end of orientation session.
***Payments for all study visits are paid in cash at the debriefing session.**

Optional Research:

Sometimes new genetic information becomes available after a study has been completed, that would make it interesting to re-examine a different part of your DNA. Therefore if you agree, we request to store your DNA for future research and re-analysis of the data collected in this study. If you do not wish for your DNA to be used for future research, it will be discarded after the testing has been completed for this study. You may also contact Dr. Childs at any point in the future to request that your genetic sample be removed from storage and destroyed, at which point it will be destroyed. We may study some or all of your genes and the results of this genetic research will not be returned to you.

☐ I agree to allow my genetic data to be kept by Dr. Childs at the Human Addiction Psychopharmacology Laboratory for future genetic research by this research study team to learn more about how to prevent, detect, or treat drug abuse and addiction.

☐ I do not agree to allow my genetic data to be kept by Dr. Childs at the Human Addiction Psychopharmacology Laboratory for future genetic research by this research study team to learn more about how to prevent, detect, or treat drug abuse and addiction.

Initials _____.

What are the potential risks and discomforts?

Physical risks: The following is a list of the most common side effects of drugs that may be used in this study:

- Constipation
- Rapid heart rate
- Dryness of the mouth
- Confusion
- Headache
- Memory loss
- Finger/toe numbness
- Chest discomfort
- Drowsiness
- Raised blood pressure
- Changes in sex drive
- Slurred speech
- Nausea or muscle weakness
- Tiredness
- Trouble sleeping
- Anxiety
- Dizziness or faintness
- Restlessness
- Double or blurred vision
- Shakiness or tremor
- Coordination problems
- Depression
- Shortness of breath
- Diarrhea

Certain of the drugs you may receive also have the potential to be abused, but the risk of this is very low for individuals who qualify for these studies based on our careful screening procedures. The experimenter should be informed of any symptom or feeling that you associate with the drug taken for the experiment. If you experience any adverse reactions to the drugs, the experimenter may remove you from the study before completion. You should also be aware that small amounts of the drugs you receive may remain in your body for up to a week after you take them and that this could result in a positive drug test. If you intend to undergo a drug screening within one week of participating in this study, please advise the experimenter.

There is also a potential risk of pain, bruising or inflammation (the body's response to injury or irritation) at the needle site for the blood draw.

Non-physical Risks: There is a very small risk of a loss of privacy (revealing to others that you are taking part in this study) or confidentiality (revealing information about you to others to whom you have not given permission to see this information). You may experience mild anxiety or embarrassment in answering questions of a personal nature regarding your health and well-being.

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

There is a risk that someone could get access to the genetic information we have stored about you. Genetic testing can create information about a subjects' and their families' personal health risks and can cause or increase anxiety, and/or interfere with your ability to get insurance or a job, and can even lead to discrimination. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. There are laws against this kind of misuse, but they may not give full protection. There may be other unforeseen privacy risks. We believe the chance these things will happen is very small, but we cannot make guarantees. Your privacy and the confidentiality of your data are very important to us and we will make every effort to protect them. These efforts are described in the section below called "What about privacy and confidentiality?".

What are the reproductive risks?

If you are a woman, the drugs that may be administered in this study can cause harm to an unborn child. To protect against possible side effects of the study drug, if you are pregnant or nursing a child you may not take part in this study. At the start of each study session involving drug administration, you will provide a urine sample to be tested for pregnancy. The test must be negative for the session to continue.

Will I be told about new information that may affect my decision to participate?

During the course of the study, you will be informed of any significant new research information (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the research. If new information is provided to you, your consent to continue participating in this research may be re-obtained.

Are there benefits to taking part in the research?

You will not directly benefit from participation in the research. This study is designed to learn more about the factors that influence whether a person who takes psychoactive drugs may go on to abuse them and develop addiction or dependence. The study results may be used to help other people in the future.

What other options are there?

This is not a treatment study. Your alternative is to not participate in this study**.**

What about privacy and confidentiality?

The people who will know that you are a research subject are members of the research team. Otherwise information about you will only be disclosed to others with your written permission, or if necessary to protect your rights or welfare (for example, if you are injured and need emergency care or when the UIC Office for the Protection of Research Subjects monitors the research or consent process) or if required by law.

Study information which identifies you and the consent form signed by you will be looked at and/or copied for checking up on the research by the funding agency (National Institutes of Health) and /or others including UIC Office for the Protection of Research Subjects; State of Illinois Auditors, or the Food and Drug Administration (FDA).

A possible risk of the research is that your participation in the research or information about you might become known to individuals outside the research. Your personal information will not be stored with the data collected in this study. Your data collected in this study will be identified by a unique study code assigned only to you and the file linking this ID to your name will be kept separately to the data in a secure location (locked filing cabinet) in Dr. Childs' office. All data collected from participants in this study will be given to the study sponsor (National Institute of Health) to ensure that it is applicable to the general population. You will not be identified in this information provided to the study sponsor. Personal information collected from you during the study will be destroyed after the data is published.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

To help us protect you and the information we will be collecting from you, this study has been given a Certificate of Confidentiality by the National Institutes of Health. This Certificate means that the researchers cannot be forced, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, to disclose any information that may identify you. The researchers will use the Certificate to resist any demands of information that would identify you, except as explained below.

The Certificate cannot be used to resist a request for information from United States government employees if the request is for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate does not stop you or a member of our family from voluntarily disclosing to any person information about yourself or your involvement in the study. If you give your written consent to release study information to an insurer, employer or other person, the Certificate cannot be used to withhold this information.

If the researchers become aware that you may cause serious harm to yourself or others, the researchers may report this to the appropriate authorities without your consent.

If you disclose actual or suspected abuse, neglect, or exploitation of a child, or disabled or elderly adult, the researcher or any member of the study staff must, and will, report this to Child Protective Services (i.e. Department of Family and Human Services), Adult Protective Services, and/or the nearest law enforcement agency.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. Videotapes that are collected during the study will be viewed only by the researcher staff working on the study and will be destroyed after the study.

What if I am injured as a result of my participation?

If you get ill or injured from being in the study, UIC will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Childs at telephone number 312-355-2726

You should let any health care provider who treats you know that you are in a research study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact the research doctors.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

UIC has not set aside any money to pay you or to pay for your treatment if you get ill or injured from being in the study. There are no plans for the University to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illnesses or injuries. The only exception to this policy is if it is proven that your injury or illness is directly caused by the negligence of an UIC employee.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

What are the costs for participating in this research?

There are no costs to you for participating in this research.

Will I be reimbursed for any of my expenses or paid for my participation in this research?

You will receive $250 in cash for completing all of the visits and procedures involved in this study. If you do not complete the study, you will be compensated for the visits you have completed according to the schedule in Table 1 (page 3).

Can I withdraw or be removed from the study?

If you decide to participate, you are free to withdraw your consent and discontinue participation at any time. You have the right to leave a study at any time without penalty.
The Researchers also have the right to stop your participation in this study without your consent if:

- You are unable to meet the requirements of the study;
- Your medical condition changes;
- New information becomes available that indicates that participation in this study is not in your best interest; or
- If the study is stopped.

In the event you withdraw or are asked to leave the study, you will still be compensated to the extent of your participation as described above.

Who should I contact if I have questions?

You can contact Dr Childs at 312-355-2726 or at echilds@uic.edu :

- if you have any questions about this study or your part in it,
- if you have questions, concerns or complaints about the research.

What are my rights as a research subject?

If you feel you have not been treated according to the descriptions in this form, or if you have any questions about your rights as a research subject, including questions, concerns, complaints, or to offer input, you may call the Office for the Protection of Research Subjects (OPRS) at 312-996-1711 or 1-866-789-6215 (toll-free) or e-mail OPRS at uicirb@uic.edu.

What if I am a UIC student?

You may choose not to participate or to stop your participation in this research at any time. This will not affect your class standing or grades at UIC. The investigator may also end your participation in the research. If this happens, your class standing or grades will not be affected. You will not be offered or receive any special consideration if you participate in this research.

What if I am a UIC employee?

Your participation in this research is in no way a part of your university duties, and your refusal to participate will not, in any way, affect your employment with the university, or the benefits, privileges, or opportunities associated with your employment at UIC. You will not be offered or receive any special consideration if you participate in this research.

Remember:
Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

Signature of Subject
I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to participate in this research. I will be given a copy of this signed and dated form.

_____ _____
Signature Date

_____
Printed Name

_____ _____
Signature of Person Obtaining Consent Date (must be same as subject's)

_____
Printed Name of Person Obtaining Consent