EFFECTS OF SMOKING ENVIRONMENTS ON BRAIN REACTIVITY

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PURPOSE

The goal of this study is to evaluate correlations between brain reactivity (as assessed via fMRI following 24-h abstinence) and the amount of smoking in a specific location. We will use ecological momentary assessment (EMA) to ask smokers to rate their exposure to, and smoking in, specific personal smoking environment cues (PSEs) over the course of 2 weeks before quitting smoking and 2 weeks after quitting smoking. Establishing that such correlations exist will provide strong evidence on the functional neuroanatomy of drug-context memory formation and retrieval.

BACKGROUND

Encountering an environment in which smoking has regularly occurred and/or its effects experienced, triggers strong craving and promotes lapse or relapse in smokers who have quit. Clinicians and recovery programs have long recognized the powerful influence of drug-environment associations and counsel patients to avoid “people, places, and things” associated with prior use. Confirming these intuitions, real-world assessment (i.e. ecological momentary assessment) of smoking suggests that relapse most often occurs in environments previously associated with smoking and that abstaining in contexts associated with smoking decreases the probability of later lapse.

Despite recognition of the influence of environment as a determinant of drug use and relapse, and despite a large and growing preclinical literature, surprisingly little empirical work has specifically addressed questions around drug-environment associations in humans. Laboratory-based studies have demonstrated that environments previously unassociated with smoking, when paired with or made predictive of smoking, can elicit urges to smoke. More recently, preference for a room paired with a low dose of amphetamine has been demonstrated in amphetamine-naïve subjects and has been suggested as a human analog of conditioned place preference (CPP). Collectively, this and other cue-conditioning research in humans provides insight into the formation of drug-environment associations but leaves open questions regarding the influence of *real-world environments* on subjective experience, behavior and brain function among individuals with long drug use histories.

DESIGN AND PROCEDURES

We propose to obtain consent from a total of 200 participants in order to identify 48 who meet all inclusion and exclusion criteria and complete all aspects of the study. During a phone screening interview, the study will be described in detail and preliminary participant characteristics (e.g. age, number of cigarettes per day) will be assessed. Those participants who meet criteria for participation will be invited to our offices for an informed consent and screening visit.

Screening session. During screening, all aspects of the study will be described to subjects and informed consent will be acquired. Breath and saliva samples will be collected in order to verify smoking status and blood alcohol level (BAL); and measures including, but not limited to, smoking

history, nicotine dependence, and mood will be collected. Vitals such as heart rate, blood pressure and weight/height will also be measured. Urine samples will be obtained in order to screen for illicit drug use and pregnancy status. Use of illegal drugs will be exclusionary. Marijuana use will not be exclusionary, but participants must agree to not use marijuana 24 hours prior to sessions and may not mix their marijuana with tobacco (i.e. blunts). Females who test positive for pregnancy will be excluded from the study and be given options for smoking cessation programs. Participants will also be interviewed regarding their smoking behavior including an assessment of contexts (places) in which they smoke and abstain from smoking cigarettes.

Inclusion criteria:

1) generally healthy [(i.e. ambulatory, not currently sick)]
2) between the ages of 18 and 65
3) smoking of at least 5 cig/day of a brand delivering ≥ 0.5 mg nicotine (FTC method) for ≥ 1 year
4) an expired CO concentration of at least 10 ppm (to confirm inhalation) or urinary cotinine >1000 ng/mL (NicAlert = 6).
5) interest in quitting smoking within the timeframe of the experiment.
6) ability to identify 4 personal smoking and 4 personal non-smoking places.
7) right handed as measured by a three-item scale used in our laboratory
8) own a smartphone
9) Breath Alcohol Level =0.000

Exclusion criteria:

1) immediate or no desire to quit smoking;
2) inability to attend all required experimental sessions;
3) use of other tobacco products or e-cigarettes more than 9 days in the past 30 days;
4) current alcohol or drug abuse;
5) positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, and PCP
    a. marijuana will be tested for but will not be exclusionary;

    b. participants failing the toxicology screen will be allowed to re-screen once;
6) current use of psychoactive medications per self-report or urine screen
7) current use of nicotine replacement therapy or other smoking cessation treatment;
8) screening systolic BP greater than 140 (participants failing for blood pressure will be allowed to rescreen once)
9) screening diastolic BP greater than 90 (participants failing for blood pressure will be allowed to rescreen once)
10) screening heart rate greater than 100 (participants failing for heart rate will be allowed to rescreen once)
11) presence of conditions contraindicated for nicotine replacement therapy (e.g., skin allergies)
12) report of significant health problems including but not restricted to (e.g. chronic hypertension, emphysema, seizure disorder, history of significant heart problems, heart disease, heart attack in the past 90 days, irregular heartbeat)
13) medical condition that may contraindicate participation in the opinion of the investigator and study physician.
14) current major psychiatric disease such as schizophrenia or schizoaffective disorder
15) currently pregnant, breast feeding or likely to become pregnant;
16) a quit attempt resulting in greater than 3 days of abstinence in the past 30 days
17) presence of conditions that would make MRI unsafe (e.g., pacemaker)

17) problems with vision that cannot be corrected with contacts or glasses

Among females, pregnancy at screening as measured by a urine test will be exclusionary. Females of child bearing potential must agree to use appropriate contraception during the course of the study. They must further agree to notify the study staff if they become pregnant during the study. If the urine pregnancy test is negative and subject meets all other inclusion criteria, an additional urine pregnancy test will be conducted at the scanning session.

Participants will be asked to indicate in the consent form whether they would like to be contacted about future studies while the present study is ongoing. Participants will be informed there is no obligation to participate and their refusal for future contact will in no way affect their participation in this study.

Training session. Participants will be introduced to the digital camera they will use to capture images of their personal environments. All information regarding the recording of events, the taking of pictures and operation of the camera (e.g. recharging, storage) will be reviewed with the participant. Any questions from participants regarding the use of the camera will be discussed. Participants will also be allowed to take photos with their own personal devices and email them to the study staff. If participants choose to take photos with device(s) other than the camera provided, the device(s) must have a photo resolution of at least 72 dpi. In addition to assessing environments and training on camera use, all participants will be placed in the mock scanner. While in the mock scanner they will be familiarized with the fMRI cue-reactivity task and GGNG task. During the training session a breath CO sample will be collected.

Camera Turn-in session. Once participants have collected at least 32 photographs of personal neutral and smoking environments, participants will return to the lab with the camera. The images from the camera will be uploaded, examined, and reviewed with each participant to ensure enough useable pictures were taken. Participants will be instructed to review and remove any pictures of other people from the camera prior to uploading. After uploading the pictures, if the study staff discover any pictures of other people those images will be permanently deleted. Pictures taken by participants will become property of the Duke Center for Addiction Science and Technology (CfAST) for research purposes. A participant's pictures of any private location, such as a home, will not be shown to any other research participants in this or any other study. Any pictures of public places (bus stop, restaurant, etc.) may be used and shown to participants in future studies.

MetricWire Mobile Application: Following the picture review, participants will be trained on how to download and use MetricWire, a mobile application (app) on a smartphone and how to answer study related questions on the app. After the Camera Turn-in session participants will be randomly prompted to answer questions, including items related to craving and mood, on the mobile app up to 6 times throughout the day. Participants will also be asked fill out a survey on the app each time they smoke a cigarette. Participants will be compensated $0.50 for each of the 6 prompted surveys completed ($3.00 maximum daily amount)

GPS Logger- Participants will carry a GPS device with them for two weeks prior to the quit date and two weeks after the quit date. The GPS logger is a small device designed to measure and record location by triangulating signals transmitted from earth orbiting satellites. The unit we will use is about the size of a cigarette lighter and is rechargeable. When operational, the GPS unit will continuously record participant location and this information will be later downloaded onto a secured server with limited access. Participants will be required to keep the GPS on and with them at all times during the 4 week period except when it might become wet (bathing, showering, swimming) or when sleeping. Participants

will be provided with detailed instructions on how to operate and recharge the unit. Participants will receive $2.50 per day for carrying the device and providing high quality GPS tracking (i.e. no evidence of leaving it in one location for the entire day). Participants will also receive a $75 bonus for 4 weeks of compliance with GPS tracking and MetricWire surveys.

Nicotine Patches:
Participants will wear Nicotine patches (Nicoderm CQ®): 21mg/day patches for 6 weeks, then step down to 14mg/d patches for 2 weeks and finally step down 7mg/d for the last 2 weeks of study protocol. If the participant smokes less than 10 cigarettes/day, we will start them on 14mg/day patches for 6 weeks before stepping down to 7mg/day patches for the final 4 weeks of treatment. Insomnia and abnormal dreams are common and expected side effects associated with 24 hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. Using 1% hydrocortisone cream on the affected area will be recommended to help reduce skin irritation. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include lightheadedness, dizziness, nausea, fainting and vomiting. Symptoms considered moderate to severe in nature will be evaluated by the study medical staff by telephone or in person, depending upon the level of severity. Upon evaluation, the subject will then be given the choice of continuing in the study while discontinuing patch use.

fMRI session. Following the picture taking phase, 1 fMRI session will take place. The fMRI session will begin following 24 hour smoking abstinence. 24 hour smoking abstinence will be verified by breath CO <6ppm. Female participants must provide a urine sample for pregnancy testing the day of the MRI scan. The test results must be negative in order to continue with the study. Prior to entering the scanner, participants will complete questionnaires regarding their current mood and withdrawal symptoms. Respiration and heart rate will be monitored during the scan to collect physiological data. Standard localizer and anatomical scans will be conducted followed by fMRI scanning. During fMRI scanning, participants will view pictures of personal and standard smoking and non-smoking environments; and also pictures of smoking-related (cigarettes, lighters, ashtrays) and non-smoking related objects (keys, tape dispensers, pencils). Participants will also complete a Go/Go/No-Go task consisting of three types of trials: frequent-Go, infrequent-Go, and No-Go trials. In the frequent-Go and infrequent-Go trials, subjects are required to press a button as quickly as possible, whereas in the No-Go trials, subjects are to refrain from pressing the button. For each trial, a colored circle is presented. The color of the circle indicates the type of trial: gray indicates a frequent-Go trial, and yellow or blue indicates the infrequent-Go or No-Go trial. The relationship between color (yellow/blue) and trials type (infrequent-Go/No-Go) is counterbalanced across subjects. After being removed from the scanner, participants will complete post-session mood and withdrawal questionnaires.

Breath alcohol levels will be assessed prior to the fMRI session and participants must record a BAL of 0.000. Participants who test positive for alcohol will be excluded from participation that day and asked to reschedule. Participants testing positive for alcohol on more than one occasion will be excluded from the study.

Lab Visits: Four lab visits will be conducted during the 10 weeks following the quit day. The visits will take place 1 week, 2 weeks, 6 weeks and 10 weeks post quit day. Each visit will have a window period of +/- 3 days from targeted date, calculated from date of camera return visit. Visits exceeding the window period will be recorded as a protocol deviation. These visits will be largely identical except that instructions and reminders to participants about upcoming events will vary from session to session. At each lab visit the following will be collected: vitals (heart rate, blood pressure and weight), breath CO and measures of smoking withdrawal and mood. Nicotine patches and instructions for using them will

be provided at each session. Advice on quitting and minimal support will be provided as requested at these visits. During the third lab visit participants will review and annotate their GPS tracks with study staff by indicating the name (e.g. home, work, library) of stay-points (i.e. places they spent more than 1 hour). Each lab visit will require 20-30 minutes of participant time.

6 month Follow-Up phone call. Participants will be contacted by phone 6 months after completing the study to complete a brief interview about current smoking status and nicotine dependence.

DATA ANALYSIS

The primary aim of the study is to examine differences in brain responses to personal vs. standard smoking and non-smoking environments. Multiple methods will be used to test hypotheses about brain functioning during cue-reactivity (CR): a region of interest (ROI) based approach for testing specific *a priori* hypotheses and a voxel-wise whole-brain analysis for identifying unexpected findings. This two-pronged approach to fMRI data analysis will allow us to maximally evaluate variability in signal over space and time while minimizing the risk of both Type I and II error. For each hypothesis, the brain CR variable of interest will be the difference in mean % signal change. We will examine correlation between brain responses to smoking environments (minus non-smoking environments) and smoking cessation outcomes (i.e. days to lapse, days to relapse).

Our EMA+GPS analysis will primarily focus on locations where smokers smoke before and after quitting smoking. We will first examine whether post-quit craving and lapse behavior occur in locations associated with smoking prior to quitting smoking. Moreover, we will evaluate whether being in locations associated with prior smoking (but not smoking) during the post-cessation period are associated with better treatment outcomes. Finally, based on GPS location and self-reported EMA location, we will assign smoking intensity values to personal smoking environments presented in the scanner. We will evaluate whether EMA-assessed smoking intensity values are correlated with brain responses to these personal smoking environments.

RISK/BENEFIT ASSESSMENT

Nicotine Patch: Insomnia and abnormal dreams are common and expected side effects associated with 24 hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. Using 1% hydrocortisone cream on the affected area will be recommended to help reduce skin irritation. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include, lightheadedness, dizziness, nausea, fainting and vomiting. Symptoms considered moderate to severe in nature will be evaluated by the study medical staff by telephone or in person, depending upon the level of severity. Upon evaluation, the subject will then be given the choice of continuing in the study while discontinuing patch use.

Women of childbearing potential: Pregnant or nursing women will be excluded from the study. Female participants will undergo a urine pregnancy test at screening. Subjects must also agree to use appropriate contraception during the course of the trial. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular

event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking. They will be encouraged in the consent form to notify study staff if they believe a change in their pregnancy status has occurred during the trial.

Management of side effects: Reports of side effects will be obtained by study staff and communicated to the principle investigator and study physician, who will determine the most appropriate course of action, which may include options for termination of study participation. Participants will be reminded of their option to withdraw from the study at any time. If a participant decides to withdraw from the study, we will ask them to return for a final visit to return all study materials. In the event of significant side effects it will be necessary to reduce patch dosage. In response to complaints of insomnia, instructions will be given to remove skin patches at bedtime. In the event of other intolerable side effects patches will be discontinued completely.

MRI: MRI provides clinically relevant anatomic and functional information non-invasively and with minimal risk, if the well-known contraindications (such as pacemakers) and potential hazards (such as attraction of metallic objects) are avoided.

Do you feel that there is any risk to wearing the GPS tracker and having their whereabouts known? I recognize that smart phones and activity trackers have this feature, but you are specifically providing them with a GPS tracker for tracking purposes for the study.

PARTICIPANT RECRUITMENT AND COMPENSATION

We will advertise in local newspapers, the radio, tv, flyers on bulletin boards, Facebook and on the internet (including but not limited to trianglesmokingstudies.com and craigslist). When we receive calls from potential subjects we will return their call and ask information including name, address, age, and smoking history. They will be given a brief description of our studies and will be asked questions to determine interest and eligibility. If they do qualify we will schedule a screening session where we will follow all IRB protocols of informed consent.

We will utilize medical records querying systems to identify and pre-screen possibly eligible subjects. After a report is generated from the medical records of patients meeting our defined criteria, they will be sent an invitation to participate in the study through their Duke patient portal. Patients can indicate on the portal whether or not to seek more information about the study which will send a communication to the research team. Those who indicate interest in participating will be contacted by the research team to proceed to the initial phone screening phase (as described above).

Participants will receive $25 at the screening session if they pass the drug test, breath alcohol test and CO test. Individuals who do not pass these tests will be dismissed from the screening visit without payment, except in the event they can produce a current, valid prescription for the medication that caused them to fail the drug test. Participants will also receive $25 for completing the training session, $25 for the camera return visit plus $25 if they returned complete and useable photos within one week of the training session, $100 for the fMRI session, $30 for each post-quit lab visit ($120 total) and a $100 at the end of the study if they complete all sessions (up to $420 total). Participants may also earn $5.50 each day they complete their MetricWire surveys and GPS logging, with a $75 bonus for 4 weeks compliance with GPS tracking and MetricWire surveys.(up to $229). Participants will also receive $10 for completing a 6 month post quit date follow-up phone call. Participants that decide to withdraw from

the study before fulfilling all of the requested tasks will be given compensation for completed study tasks.

DATA AND SAFETY MONITORING

The Principal Investigator will report all serious adverse events and unanticipated findings and problems relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with standard operating procedures.

COSTS TO PARTICIPANTS

There are no costs to participants for taking part in this study. All the study costs, including any procedures related directly to the study, will be paid for by the study.

DATA STORAGE AND CONFIDENTIALITY

Participants will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations.

Except when required by law, the participant will not be identified by name, social security number, address, telephone number or any other direct personal identifiers in the study records.

All photographic images acquired by participants will be reviewable by participants prior to upload to the secure server. Data from the server can only be accessed by authorized study staff with a username and password. All photographs of private locations taken by participants will be destroyed by the PI or CRC upon completion of the study. Photographs that include persons not known to subject will be deleted. The participant will be assigned a unique code number and the key to the code will be kept in a locked room accessible to the study coordinator.

This study uses a mobile app named MetricWire to collect data. MetricWire is a company based in Canada. The data submitted in the app is stored in the United States, by a company called Amazon Web Services, which is based in Virginia. While MetricWire will not access data that is submitted using the app, they have logical access to the data. This means that it is possible that they could view the data. The study team has executed a research contract with MetricWire that has research controls embedded by the Information Security Office. Participants will be fully informed during the consent process on both the above information about MetricWire specifically and the limits of confidentiality related to the use of mobile apps more broadly.

At the initial session, study staff will log participants into the MetricWire app using a unique username and password. This username and password will be set by the study staff and will contain no identifying information. All smartphone electronic diaries and ecological momentary assessments will be treated as confidential.

Use of a personal phone: Participants who choose to use their personal smartphone for the study will receive instructions on how to install the app on their phone and study staff will assist with the installation. The study team will also provide instructions on how to remove the app from their device at the end of the study. Thus, while we acknowledge that a breach of confidentiality is possible, the likelihood is very low.

Dr. Cynthia Conklin at UPMC will be a collaborator for the study. She is listed as outside key personnel and will not have access to any study PHI or identifiable information.