Project Title: Neurobehavioral Substrates of Propranolol's Effects on Drug Cue Reactivity

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We propose to obtain consent from a total of 75 smokers in order to identify 40 who meet all inclusion and exclusion criteria and provide usable data sets. Participants will complete an initial screening either online or over the phone. In both cases, the study will be described in detail and preliminary participant characteristics will be assessed (e.g. age, number of cigarettes per day, use of exclusionary medications or medical conditions that would preclude participation). Online screenings will be administered via Duke REDCap questionnaires. Participants who complete the online screen will also be contacted by phone to confirm information and provide additional study information. Those participants who appear to meet criteria for participation will be invited to our offices for an informed consent and screening visit. Identifying information from the phone screen for participants who do not meet inclusion criteria will be kept until recruitment for this study is completed and stored on a secure department server. See Waiver of Consent and HIPAA authorization. Participants or potential participants will be provided with a copy of the drug insert upon request - either by email/postal mail in advance of participation or at their screening visit.

Screening Session

Volunteers who meet initial eligibility criteria (determined by online/phone screening) will be asked to attend an in-person screening approximately 2-3 hours in length. The PI or other study staff will give a ~10 minute presentation describing details of the study procedures and risks. They will be provided with a consent document to review and given the opportunity to ask questions. They will then obtain informed consent. Afterwards, participants will:

- Provide breath samples for expired breath carbon monoxide (CO) level analysis using a CO meter. This is a reliable and valid measure of recent smoking.
- Provide a breath sample for analysis of breath alcohol level using an AlcoSensor breathalyzer device. Participants with levels > .000 will be offered one opportunity to reschedule their visit – any further positive readings will result in exclusion.
- Urine samples will be obtained to screen for pregnancy (HCG) among female participants and illicit drug use among all participants.
- Established questionnaires will be used to assess nicotine dependence (Fagerstr m Test for Nicotine Dependence) and quit motivation (Contemplation ladder). A detailed smoking history will also be obtained.
- Additional questionnaires will be used to assess other potential moderators and variables of interest for exploratory analysis
- The MINI International Neuropsychiatric Interview will be conducted by the PI or other staff working under his supervision in order to screen for exclusionary psychopathology.
- Participants will undergo a full physical exam conducted by the study physician (Dr. Rachel Dew) to ensure safety of propranolol administration. This will include blood pressure readings and EKG. A blood sample will be drawn and submitted for analysis (CBC, basic metabolic panel and serum pregnancy [females]) and reviewed once available (prior to drug administration). Depending on scheduling and physician/psychologist availability, participants will also have the option of completing the physical exam and clinical interview at the training visit or camera return visit. These will always occur prior to randomization/drug administration.
- Complete a visual acuity exam

Certain components of the procedure (e.g. MINI, cognitive tests) may be audio recorded. Failure to meet requirements for the study will result in dismissal. Sexually active females must agree to use contraception during the course of the study and notify study staff if they become pregnant during the course of the study. Per standard procedures at the Brain Imaging and Analysis Center, an additional pregnancy test will occur at these sessions.

Training Session

Participants who did not complete a medical exam at the baseline visit will do so at this visit. In addition, they will be exposed to a "mock" MRI scanner and asked to complete an abbreviated picture viewing task so that they can experience the scanner environment and ensure they are comfortable completing MRI sessions. Eligible participants will be trained in the picture-taking procedures, provided a camera if they do not own a suitable one and scheduled to return in approximately one week. They will be asked to take > 5 photographs of smoking and non-smoking environments as identified during interviews.

Camera Return Session

Participants will return the camera they were provided. Images will be downloaded and reviewed for appropriateness. If necessary, they will be given additional time to obtain appropriate images. If images are deemed appropriate, the participant will be scheduled for an MRI session. In addition, participants will complete a brief "Environment Go-NoGo task." This is a modified version of the standard Go-NoGo task. Stimuli (letters, numbers or symbols) will be embedded in images consisting of smoking (e.g. bus stop) or non-smoking (e.g. church) environments. Participants will view blocks of these stimuli be instructed to identify a the presence of a particular stimulus by button press. .

fMRI Session

Participants will be required to be 24 hours abstinent at the time of the scan as indicated by a breath CO level < 8 ppm. Participants will also be tested for breath alcohol and must record a BrAC of < 0.001. Participants who do not meet the CO level may be provided one opportunity to reschedule at the discretion of the PI or study staff. Participants who are unable to attain the required CO level will be withdrawn. Participants will be instructed to eat 1 hour prior to their appointment in an effort to standardize drug absorption. Research staff will meet participants at the scanning facility. Drug will be stored in a secure closet in our laboratory and walked over to the hospital for administration during the scanning session. CO will be collected upon participant arrival. Afterwards, participants will be randomly assigned to propranolol (40 mg) or placebo conditions. These will be administered 1.5 hours prior to scanning. Heart rate and BP will be monitored every 45 minutes during the intervening period. Self-report assessments of craving (Questionnaire on Smoking Urges – Brief) and nicotine withdrawal (Minnesota Nicotine Withdrawal Scale), among other measures, will be obtained immediately prior to drug administration and again immediately prior to scanning. During the scan, participants will be positioned in a 3T MRI scanner and completing a resting scan, anatomical scan and several function runs during which they will view images of the environments they photographed, as well as standard smoking/non-smoking environments and proximal smoking/neutral cues. Heart rate and respiration will be monitored during resting tasks. Respiration will be monitored during all tasks.

Laboratory Session

Participants will attend a final laboratory session. They will be required to be 6 hours abstinent at the time of the session as indicated by a 40% reduction in breath CO from the value obtained at the screening session. Participants will also be tested for breath alcohol and must record a BrAC of < 0.001. As above, participants who do not meet the CO level may be provided one opportunity to reschedule at the discretion of the PI or study staff. Participants who are unable to attain the required CO level will be withdrawn. Next, they will repeat the previously administered craving/withdrawal measures. As with the MRI session, participants will be instructed to eat 1 hour prior to their appointment in an effort to standardize drug absorption. A second dose of propranolol or placebo will be administered 1.5 hours before the cue exposure task. As above, heart rate and BP will be monitored during the intervening period and self-report assessments of craving and withdrawal will be obtained immediately prior to beginning the task. The task will consist of an initial 2-minute cue exposure period, followed by an additional craving assessment. Next, participants will view cues for an additional 12 minutes during which they will have *ad libitum* access to their cigarettes and are informed they may smoke freely. Participant behavior will be video recorded during this period for later coding by video. After the *ad lib* smoking period, participants will complete an additional set of measures, as well as an additional CO assessment. At the conclusion of this session, participants will meet with the PI or staff working under his

supervision. They will be provided with the smoking behavior report, psychoeducation about smoking behavior and the importance of cessation, and a list of referrals. In addition, they will be provided with a stack of study recruitment materials and encouraged to distribute them to family and friends who smoke as typical of a snowball sampling approach. However, per Duke IRB policy, no incentives will be offered for distributing these materials.

Statistical Analysis Plan

Analyses will examine the effects of propranolol: (1) BOLD activation and connectivity in response to smoking cues; (2) Smoking urge in response to smoking cues during the MRI task; (3) Smoking urge in response to personal smoking environment cues during the laboratory task; and (4) Smoking behavior during the laboratory smoking task.

Primarily analyses of BOLD activation results will utilize and ROI-based approach. Percent signal change in response to all cue types will be extracted from the hippocampus (both posterior and anterior), amygdala, medial prefrontal cortex and anterior insula. Extracted values will then be examined using SPSS mixed models, utilizing repeated statements in lieu of random effects (analogous to repeated measures ANOVA). A compound symmetry covariance structure will be specified. Analyses will examine the effects of drug condition on cue reactivity. For BOLD Activation, our primary outcome will be the overall smoking cue reactivity effects (i.e. collapsing across image type – proximal, standard environment, personal environment) although planned contrasts will break these down by individual image types to clarify effects. In addition, we will use a psychophysiological interaction approach to extract indices of brain connectivity while viewing smoking-related images. We anticipate using a hippocampus seed based on pre-clinical findings, but a final determination will be based on the pattern of activation observed in the present study. Any baseline group differences will be adjusted for in these analyses. Connectivity between the seed region and other relevant brain regions (same as above) will also be examined. An identical approach will be used to examining smoking urge during the MRI task.

Smoking urge and behavioral outcomes for the laboratory task will be analyzed using similar procedures. First, video data will be coded by two independent raters. Substantive disagreements will be resolved through discussion, the average value will be taken when minor disparities are present. For self-reported urge, analyses will examine drug effects on post-cue-presentation urge ratings (again, adjusting for any baseline group differences, as well as pre-cue-presentation urge rating). Analysis of behavioral outcomes will follow a similar approach – although a variety of indices of smoking behavior will be computed our primary focus will be on the total number of puffs taken across the *ad lib* smoking period (aggregated across cigarettes when relevant).