

Study Title: Effects of smoking state on effort-based decision making (Effort Pilot) IRB# 79949

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Background and Rationale

Dopamine modulates effort expenditure and reward sensitivity, which are specific components of motivation [1]. Effort expenditure is costly, and effort-based decisions weigh the value or preference of a reward, as well as the likelihood of receiving it, against the amount of effort needed to obtain it [2, 3]. Effort-based decisions are typically studied in both animal models and humans using paradigms that offer a choice between a low-effort/low-reward option and a high-effort/high-reward option [4]. Preclinical and clinical studies have shown that increasing or decreasing striatal DA transmission via drugs, DA depletions, or genetic manipulations can enhance or diminish (respectively) effortful responding for a reward, especially when a large amount of effort is required to obtain it [5-10]. Importantly, the hedonic value of the reward does not appear to be affected, e.g., rodents with DA depletions/antagonists still prefer highly-palatable foods to standard chow and maintain low-effort responding for palatable food and its consumption [1]. Striatal DA appears to be signaling the motivational influence of a potential reward on taking action to obtain it, and this signal incorporates effort costs when those costs affect the overall reward rate [11]. More precisely, DA is believed to couple effort expenditure to expected reward value, such that diminished DA promotes effort conservation and favors rewards that are larger and more certain (i.e., increased reward sensitivity), whereas enhanced DA promotes effort expenditure and tolerates rewards that are smaller and less certain (i.e., decreased reward sensitivity) [12, 13]. Healthy DA function helps individuals maximize the expected value of rewards and minimize the effort expended to obtain them. Either too much or too little reward sensitivity could result in poor decision making, but healthy DA function supports- depending on the situation- effort expenditure for low-value, delayed, or uncertain rewards. The ability to expend effort with some degree of flexibility regarding reward value (e.g., giving one's best effort on a math test for which there is no direct incentive for performance) is an important feature of healthy decision making that may be impaired in psychiatric disorders marked by DA dysfunction and high reward sensitivity, such as substance use disorders.

Nicotine, the primary addictive chemical in tobacco, binds to nicotinic acetylcholine receptors on DA neurons and acutely enhances DA signaling. Chronic tobacco use results in an upregulation of nicotinic acetylcholine receptors and a downregulation of DA receptors and transporters. Withdrawal from nicotine, which begins as early as 2 hours after the last cigarette and can last for several weeks, is associated with diminished DA signaling [14]. Previously, we investigated differences in effort-based decision making among smokers, ex-smokers, and non-smokers [15]. Overall, participants selected more high-effort options as potential reward magnitude and expected value increased. Smokers did not make fewer high-effort selections overall, but smokers were less sensitive to the changes in magnitude, probability, and expected value compared to never-smokers. Smokers were also less sensitive to the changes in probability and expected value, but not magnitude, compared to ex-smokers. Among smokers and ex-smokers, less nicotine dependence was associated with an increased likelihood of high-effort selections. Potentially, improved sensitivity to rewards among ex-smokers may be a cause or consequence of smoking cessation. These findings may help explain why some smokers are able to achieve long-term abstinence. Smokers had recently smoked at the time of testing, so the role of smoking state (smoking satiety versus abstinence/withdrawal) is unknown. Withdrawal-induced changes in reward sensitivity and effort-based decision making may be an important contributor to relapse among smokers making a quit attempt.

This pilot study will recruit smokers who will complete a measure of effort-based decision making during functional magnetic resonance imaging (MRI) on two occasions: following smoking as usual (satiated) and after overnight abstinence (withdrawn). They will also complete measures of distress tolerance, which complements ongoing research on the stress-smoking relationship (i.e., the parent R21 that covers the cost of this pilot study).

Specific aims:

1) Investigate the effects of smoking state on effort-based decision making and its neural correlates. Hypothesis: Compared to the satiated state, smokers in a withdrawn state will make fewer high-effort selections and will be more sensitive to expected reward value on measures of effort-based decision making.

2) Investigate the effects of smoking state on distress tolerance behavior. Hypothesis: Compared to the satiated state, smokers in a withdrawn state will have shorter durations on measures of distress tolerance.

Study Design and Procedures

Overview. Adults (aged 18-55) who smoke cigarettes (≥ 5 cigs/day for ≥ 2 years) and/or electronic nicotine delivery systems (ENDS) daily will be invited for three, 3-hour in-person sessions. The first study visit will test for eligibility. The second two visits will consist of an MRI scan, some additional behavioral testing, and self-report questionnaires. Participants will be instructed to smoke as usual before one MRI study visit (satiated state) and to abstain from using all tobacco/nicotine for at least 12 hours before the other MRI study visit (withdrawn state). The order of the satiated and withdrawn study visits will be randomized and counterbalanced across participants. The two MRI study visits will take place between 2 and 14 days apart. The study visits will take place in Dr. Addicott's lab in One Technology Plaza and in the MRI center on the main campus.

Recruitment/Screening Visit: We will advertise on internet, flyers, word of mouth, and in newspapers for volunteers for the study. Participants who qualify over the phone and are interested in participating will be scheduled for further screening at the study site. We are submitting a HIPAA Waiver for the purposes of conducting this phone screen. The in-person informed consent and screening will last about 3 hours. All aspects of the study will be described and informed consent will be obtained by the PI or study coordinator. Detailed inclusion/exclusion criteria are described below in the Study Population section.

Breath and urine samples will be collected in order to screen for drug use and recent alcohol use. Urine samples will be frozen for future testing of nicotine and nicotine metabolites (cotinine and 3-hydroxycotinine). Women of child-bearing potential will undergo urine pregnancy testing. Participants will complete an MRI safety checklist and a visual acuity test.

A saliva sample will be obtained on the Screening visit. The saliva sample is optional, and does not affect participation or compensation. The saliva sample will be banked for future analysis (e.g., DNA methylation). Samples will be labeled with the participant's study ID number and kept in the Dr. Addicott's lab. Dr. Addicott and study staff have control of the samples. The samples will be stored up to 7 years past the IRB end date of the study.

Participants will practice the physical and effort based decision making tasks.

As part of the screening, participants will undergo structured interviews, which include:

- Cigarette/e-cigarette/other tobacco use history interviews
- Tobacco use time-line follow-back interview
- MINI International Neuropsychiatric Interview (v7.0.2) to assess the current and lifetime presence of other Axis I disorders that would be exclusionary.
- Drug use history interview.

As part of the screening, participants will complete questionnaires, which include:

- Tobacco use disorder questionnaire.
- Education level/socioeconomic status questionnaire.
- CESD – Center for Epidemiologic Studies Depression Scale. Used to measure symptoms of depression
- SCAARED – Adult Anxiety Screen. Used to measure symptoms of anxiety.
- SHAPS – Snaith-Hamilton Pleasure Scale. Used to measure symptoms of anhedonia.
- DTS - Distress Tolerance Scale. Used to determine distress tolerance.
- MPQ – Multidimensional Personality Questionnaire. Used to determine motivation and control-related personality traits.

COVID-19 Precautions. Prior to being invited to any in-person session, prospective participants and participants will be asked over the phone 1) Have you had a fever, cough, or shortness of breath in the last 7 days? 2) Have you had vomiting and/or diarrhea in the last 7 days? 3) Have you had contact with someone who was diagnosed with COVID-19 within the last 2 weeks, or have been diagnosed with COVID-19 within the last 3 weeks? The same questions will be asked upon arrival in addition to a temperature check. Only participants who respond negatively to all questions and has a temperature below 99.9F will proceed with the scheduled visit. Participants and study staff will be masked during the visit. Participants will self-administer breath tests behind a glass partition in an unused office. Social distancing will be used as much as possible.

Study Visit. The study visits will last about 2-3 hours each. Expired breath samples will be tested for CO and alcohol. The study day will consist an MRI scan (about 60 min long), behavioral tests, a breath-holding test, and questionnaires. Participants will arrive 1 hour before the MRI scan to complete these measures.

During the MRI scan, participants will be administered an anatomical run and the scanner version of the physical and cognitive effort tasks.

Behavioral tests include:

- **Effort Expenditure for Reward Task (EffRT).** This MRI task measures effort-based decision making. On each trial, participants choose between two different task difficulty levels to obtain monetary rewards. Each trial offers a choice between two levels of difficulty: a “hard” task and an “easy” task. In the physical effort version, participants make repeated manual button presses within a short amount of time. Hard task trials require participants to make button presses using the non-dominant little finger, while easy task trials require participants to make button presses using the dominant index finger. In the cognitive effort version, participants see a number flashed in the middle of the screen, one number at a time. Hard task trials require participants to mentally add the number currently onscreen with the number immediately previous and indicate the sum from an array of numbers onscreen. Easy task trials require participants to indicate if the number is odd or even. Completion of easy task trials will earn 1 point. Hard task trials could earn between 1 and 5 points. However, the probability of earning the points for successful task completion is 88%, 50%, or 12%. The probability of earning points is indicated onscreen at the start of each trial. At the end of each trial, participants are shown whether they completed the task on time or not, and earned the points or not.

Each task lasts about 14 min. The points they earn during the task will go towards a \$5 bonus for each task (\$10 total per visit).

- Paced Auditory Serial Addition Test (PASAT). In this task, participants see a number flashed in the middle of the screen, one number at a time. They are instructed to mentally add the number currently onscreen with the number immediately previous, and use a computer mouse to indicate the sum from an array of options onscreen. The numbers onscreen flash quickly, and late or incorrect responses result in a loud buzzing noise. There is a simple practice task before the experimental task. In the experimental task, participants can end the task at any time, but the longer they persist in the task the more points they earn. The points they earn go towards a \$2 bonus. The duration (in min) before quitting the task is the primary behavioral measure of distress tolerance. This task lasts up to 20 min.
- Breath-holding test. Breath-holding duration will be assessed by asking participants to hold their breath for as long as they can. Duration will be measured with a stopwatch. A longer duration represents greater physical distress tolerance. The longer they persist the more points they earn. The points go towards a \$2 bonus.
- Mirror Tracing Task. In this task, participants use a computer mouse to move a cursor around a monitor to trace over a star shape without leaving the shape's lines. The mouse is programmed to move the red dot in the reverse direction. If the participant moves the red dot outside of the lines of the star, or stalls for more than 2 sec, the red dot returns to the starting position and there is a loud buzzing noise. There is a simple practice task before the experimental task. In the experimental task, participants can end the task at any time, but the longer they persist in the task the more points they earn. The points they earn go towards a \$2 bonus. The duration (in min) before quitting the task is the secondary behavioral measure of distress tolerance. This task lasts up to 20 min.

As part of the study visits, participants will complete questionnaires, which include:

- MNWS – Minnesota Nicotine Withdrawal Scale. Used to measure withdrawal symptoms.
- PSS – Perceived Stress Scale. Used to measure control of stress.
- LSC – Life Stressor Checklist. Used to measure lifetime history of past and recent life events.
- Hassle Scale. Used to measure daily hassles experienced in a typical week.
- PP – Persistence and Perseveration Scale. Used to measure perceived perseverance in everyday life.
- SUPPS-P – Short UPPS-P Impulsive behavior scale. Used to measure impulsive traits.
- WISDM – Wisconsin Inventory of Smoking Dependence Motives. Used to measure reasons for smoking.

Compensation: Participants will receive no payment for the phone screening and first hour of in-person eligibility screening. Participants will be compensated \$100 for the remainder of the study visit, and \$100 per MRI study visit (\$300 total). They can earn up to \$16 per MRI study visit as a performance bonus (\$32 total). For completing all parts of the study, participants can earn between \$300 and \$332. If a participant decides to end the study early, or is determined to be ineligible >1 hour into the eligibility visit, they will be paid \$20/hour for the time they

participated. Participants will be paid by check at the completion of the study.

Study Population

Subjects will be adult tobacco users. We anticipate consenting/screening 30 people in order to get complete and useable data from 19 subjects.

Inclusion Criteria

- 1) Aged 18-55 years
- 2) Smoke ≥ 5 cigarettes/day of a brand delivering ≥ 0.5 mg nicotine (FTC method) or vape a comparable amount of nicotine-containing e-liquid
- 3) Smoked ≥ 2 years
- 4) Expired breath CO concentration ≥ 5 ppm (unless they are primarily ENDS user)
- 5) Negative urine drug screen for illicit psychoactive drugs (excluding cannabis/THC) and negative breath alcohol concentration. Prescription drug use that has been dose stable for > 1 month, and no changes in drug use or dose expected during the study, is allowed.

Exclusion Criteria

- 1) Have an unstable medical condition, stable medical condition, or undergoing treatment for a condition that would interfere with participation, or would cause significant distress in day-to-day life, such as cancer, chronic pulmonary disease, or coronary artery disease.
- 2) History of serious head trauma or neurological disorder (e.g., seizure disorder), brain tumor, increased intracranial pressure or impaired consciousness.
- 3) Past or current psychotic disorder (e.g., schizophrenia or bipolar disorder), current major depressive disorder, or any current psychiatric problems that cause significant distress and interfere with ability to function at home, work, school, or in relationships and/or use of anti-psychotics, lithium, or second-line treatments for depression/anxiety. Psychiatric symptoms that are controlled by first-line treatments for depression/anxiety (e.g., SSRIs) are not exclusionary.
- 4) Severe substance use disorder (score of 6 or greater on MINI) in past 6 months for any drug of abuse (other than nicotine)
- 5) Current daily use of nicotine replacement therapy, or other smoking cessation medication (e.g., varenicline, bupropion)
- 6) Among females, pregnancy
- 7) Presence of conditions that would make MRI unsafe
- 8) Having vision that cannot be corrected to 20/40
- 9) Inability to attend all study sessions
- 10) Weight > 350 pounds (maximum allowed for the MRI scan)
- 11) $< 8^{\text{th}}$ grade education
- 12) Use of cannabis/THC > 4 days/week and/or more than 3 grams/week

Risks and Benefits

Women of childbearing potential: Due to unknown risks and potential harm to the unborn fetus caused by nicotine, women of child-bearing potential will be screened with urine pregnancy tests. Positive pregnancy tests are exclusionary.

Magnetic resonance imaging (MRI): There are no known long-term health risks to the use of magnetic resonance imaging per se when operated within FDA guidelines. However, there are safety concerns posed by the strong magnetic fields used to make images. All scans conducted

under this protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

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. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask participants about metal within their bodies. Participants will wear ear plugs to protect their hearing. There is also a risk of claustrophobia while being in the scanner.

Incidental MRI Findings: It is possible that this study will identify information about a subject that was previously unknown. Importantly, the research dedicated 3T scanner and the protocols used to collect these images are not for clinical purposes and diagnoses may not be possible given the scanning parameters. Nevertheless, the research staff will review all structural images as they are collected. If an abnormality is detected, the neuroimaging data will be reviewed by a neuroradiologist. Such incidental findings, if any, will not be shared with the subject unless the neuroradiologist recommends medical follow-up treatment. If so, study staff will contact the participant and inform them of the finding. In this case, the PI will not provide any diagnosis, rather the participant will be informed that, "During the course of our research scanning we have identified potential difference in your brain structure that we believe warrants follow-up with your health care provider. The brain scan image that we [can or have] provide[d] you was collected following a research protocol that may not be of the quality your doctor needs to make a final diagnosis. This will be determined by your doctor. At this point in time we cannot say that the difference we have detected is clinically significant or not. We do not mean to alarm you, but we do feel that you should follow-up with your health care provider."

Costs to subjects: Subjects will not incur any costs associated with participating in the study. All the study costs, including any procedures related directly to the study, will be paid for by the study.

Confidentiality: There is a potential risk of loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

Distress tolerance measures: There may be some physical or affective discomfort during the performance of the distress tolerance tasks. Participants are allowed to end each task at their discretion.

Drug testing: The drug test and drug use history could indicate that participants have used an illegal drug. Research funded by the National Institutes of Health protects participants' privacy by limiting the disclosure of identifiable, sensitive information. As of October 1, 2017, the NIH automatically covers NIH-funded research with certificates of confidentiality.

Nicotine withdrawal: Overnight abstinence can cause symptoms of nicotine withdrawal. These include cravings, urges to smoke, irritability, difficulty concentrating, restlessness, increased appetite, anxiety, and depressed mood.

Genetic information: Participants will be protected against a loss of confidentiality as described above. Additional protections include providing an opt-out option for the saliva sample/genetic testing. There are currently no genetic tests planned, saliva samples will be banked for future testing. DNA methylation tests may be performed. The results of genetic testing will not be revealed to the participants.

Mental health status. Participants' responses in the mental health interview may indicate a current concern for their well-being. If a study participant reports they are considering suicide, we will call 911 to transport the participant to the emergency department. Participants who are revealed to have severe mental health disorders (e.g., depression) within any questionnaire or structured interview will be encouraged to make an appointment with their healthcare provider and will be withdrawn from participating.

Benefits. There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the principal investigator's office. Only the study coordinator will have access to the code and information that identifies the subject in this study. Imaging data will be stored on a secure server and identified with the unique identifying number. At the conclusion of the study, the data will be permanently de-identified and retained for a minimum of six years after final reporting or publication of the project.

Data Analysis

Sample size. Because this is a pilot study, our statistical analysis will employ estimation, not statistical null-hypothesis tests. Statistical analyses will be conducted using SPSS with significance threshold set to $\alpha < 0.1$, given the exploratory nature of the study and the small sample size. Independent and dependent variables will be tested for normal distributions, linear relationships, homoscedastic residuals, and the absence of multicollinearity.

Aim 1) Investigate the effects of smoking state on effort-based decision making and its neural correlates. Hypothesis: Compared to the satiated state, smokers in a withdrawn state will make fewer high-effort selections and will be more sensitive to expected reward value on measures of effort-based decision making.

Effort-based decision making behavioral data will be analyzed with generalized estimating equations (GEE). GEE models take into account within-subject time-varying effects (e.g., changes in reward magnitude and probability across multiple trials) as well as smoking state. GEE models will use an autoregressive working correlation matrix. The dependent variable is the selection of high- versus low-effort tasks and a binary logistic distribution will model the probability of selecting the high-effort task. In all models, independent variables include reward magnitude, probability, expected value (magnitude \times probability), and the trial number as a nuisance covariate to control for any effects of fatigue. Separate models will test the interactions between smoking state and magnitude, probability, and expected value.

Neuroimaging data will be analyzed with SPM12 using standard preprocessing steps. First level analyses will regress task onset times onto individuals' hemodynamic response. Second level analyses will include paired-samples t-tests of brain activation differences between the smoking satiated and withdrawn states within each task (physical or cognitive effort task), as well as paired-samples t-tests of brain activation differences between the two task types. Since this is an exploratory study of brain activation as it relates to task performance and smoking state, there are no hypothesized differences between tasks or smoking states.

Aim 2) Investigate the effects of smoking state on distress tolerance behavior.

Hypothesis: Compared to the satiated state, smokers in a withdrawn state will have shorter durations on measures of distress tolerance.

Distress tolerance behavioral data will be analyzed using paired-samples t-tests for each behavioral test separately.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and Wake Forest University Health Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the WFU Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject, and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

The study will be listed on clinicaltrials.gov (NCT# 04826276) in accordance with FDA requirements.

Appendices

None

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