Self-activation of Reward-related Brain Regions in Individuals with and without Nicotine Dependence

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Purpose of the Study

To assess the ability of adults with and without nicotine dependence (ND) to activate reward-related brain areas (e.g., ventral tegmental area (VTA), striatum, prefrontal cortex (PFC)).
To evaluate whether real-time functional Magnetic Resonance Imaging (rt-fMRI) and/or real-time electroencephalography (EEG) neurofeedback improves the ability to increase reward-related brain activation in individuals with and without ND.
To examine the relationship between activation of reward-related regions via neurofeedback and dopamine availability (as assessed genetically).
To examine the effects of neurofeedback on clinically-relevant outcomes, including reward responsivity and smoking-related behaviors.

Background & Significance

Dopamine: Motivation, Learning and Adaptive Memory. A rich literature spanning diverse methods and species provides substantial evidence that the dopamine (DA) system is fundamentally involved in reward processing, motivation, learning, and memory. DA plays a critical role in facilitating long-term potentiation and maintaining long-term memories. DA is also implicated in tracking motivationally relevant information and encoding deviations between expected and received outcomes – so-called prediction errors – that drive learning. Thus, DA is critical for learning and memory formation and for guiding future adaptive behavior. Research conducted in the sponsoring laboratory was the first to demonstrate the importance of correlated activity between the midbrain and hippocampus during human learning. Healthy individuals were incentivized with rewards prior to encoding information. Correlated activity between the midbrain and hippocampus at the time of the incentive cue, but before the stimulus, predicted how well the stimulus would be remembered. That is, activation in mesolimbic regions prior to learning predicted subsequent memory success. If midbrain activation can predict improved learning, this implies that driving the DA system through instruction, a novel approach we call 'cognitive neurostimulation', has highly significant implications for both basic science and clinical applications. Understanding mechanisms of the DA system can improve reward processing, attention, motivation, working-memory, and long-term learning and memory, as well as inform personalized, safe, effective, and efficient interventions for patients with dysfunctional DA function across disease etiologies.

Real-Time neurofeedback. Real-time neurofeedback is a type of biofeedback that provides participants with information regarding their brain activity in real time. Real-time neurofeedback, which includes both rt-fMRI and rt-EEG, is a rapidly growing technique with direct application to both basic science and clinical questions. Unlike traditional fMRI or EEG studies, rt-fMRI and rt-EEG enable data to be analyzed immediately and presented to participants as a form of neurofeedback. Rt-fMRI studies have demonstrated humans' ability to modulate their own brain activity in multiple areas. Few studies have examined rt-fMRI or rt-EEG and its application to addiction and all extant rt-fMRI studies on nicotine-dependent individuals focused on reduction of activity in the cingulate cortex and prefrontal cortex. Despite the clear relationship between dopamine and addiction – to our knowledge, no study to date has examined midbrain self-activation in any addicted population. Rt-neurofeedback provides a salient demonstration to participants of how cognitive strategies can produce immediate changes in brain

function. Such a salient experience is proposed to create a strong memory of the training sessions, recruiting engagement of the medial temporal lobe (MTL). The MTL has direct connections to the midbrain, where DA neurons are located. Activation of this pathway from the MTL to the midbrain is hypothesized to increase DA release, increasing motivation, culminating in behavioral change. We predict that enhancing vivid memories of the training session will increase the frequency of subsequent self-activation and success of this technique, with the potential of improving smoking cessation outcomes in nicotine-dependent individuals.

Nicotine Dependence and Smoking Cessation. Tobacco use is the leading cause of preventable disease and death in the United States. Critically, the majority of smokers (70%) express a desire to quit smoking, but the vast minority of quit attempts (<5%) are successful long-term (> 3 months). Recent theories have proposed that failed quit attempts could in part be due to reward dysregulation in the brain that occurs with chronic drug use. Over time, repeated exposure to drugs of abuse increases subsequent reward responses to drugs and drug cues. Simultaneously, responses to non-drug rewards diminish, eventually failing to motivate behavior. This imbalance in drug versus non-drug reward responses may motivate the choice of drug stimuli over non-drug stimuli. If individuals can learn to increase the reward response to personalized, non-drug cues, it could motivate their future behavior towards non-drug stimuli. Likewise, by balancing out the reward responses to drug and non-drug cues, this may reduce the frequency and need for drug interactions, resulting in improved smoking cessation outcomes. The proposed personalized study in nicotine-dependent individuals has the potential to dramatically improve health outcomes and reduce health care cost nationwide. If successful, this protocol could readily be adapted for application to a variety of addictive disorders that act on the DA system including cocaine and other stimulants.

Research on self-activation of the DA system is highly relevant to mental health. Several neurologic and psychiatric disorders are affiliated with abnormalities in the dopaminergic system, including addiction, depression, schizophrenia, and PD2-9. The predominant treatments for these disorders include pharmacotherapy and psychotherapy. However, a current barrier to progress in the field is that for many diseases neither treatment completely cures the disorder nor alleviates the symptoms. Furthermore, pharmacotherapy is associated with adverse side effects while psychotherapy is effortful, time intensive, costly, and - perhaps most challengingly - produces effects that are not immediately apparent. Therefore patients must persist for long periods of time (e.g., days to months) without any direct indication of progress. The NIMH Strategic Research Plan demands novel interventions that are personalized, safe, effective, and efficient. This research proposal investigates the development of cognitive neurostimulation of the dopaminergic midbrain as a personalized, safe, effective, and efficient micro-intervention for nicotine-dependent individuals.

The proposed studies address fundamental unsolved problems in behavioral science and systems neurobiology. Understanding if and how rt-fMRI and/or rt-EEG neurofeedback can enable individuals with and without nicotine dependence to activate the reward-related regions will advance clinical practice by offering a novel micro-intervention for patients with dysfunctional dopaminergic systems across disease etiologies.

Design & Procedures

We will enroll up to 150 adults between 18-45 years. We will recruit up to 100 adults with nicotine dependence and 50 adults without nicotine dependence. We may need to screen additional participants in order to achieve 150 completed participants (we estimate screening 250 participants).

Prior to coming to a screening visit, all potential participants will undergo a phone pre-screening using an IRB approved phone script to pre-identify potentially eligible participants and to potentially decrease screen fail rate. These interested potential participants call or email the site in response to advertisements or provide their contact information via the internet (e.g, Facebook ad). The pre-screening will take place via phone. Participants who pass the pre-screening will complete some or all of the following visits: Screening, Camera Return Visit, Real-Time Neurofeedback Visit, Follow-up Phone Calls/Debriefing.

Screening Visit:
Participants with nicotine dependence who pass the pre-screen will come to the lab at Duke to complete additional screening. All participants will undergo informed consent. MRI participants will complete a urine drug screen. Participants who pass the urine drug screen (results are provided immediately) may complete questionnaires on REDCap assessing mood, reward processing, and smoking behaviors. We may also ask individuals with ND to complete a carbon monoxide (CO) breath test. If individuals fail to pass, they will be offered the opportunity to smoke and come back to get tested again. If they fail a second time, they will be excluded from the study. We may also ask individuals if they have consumed marijuana within the last 24 hours. If they have, the session will end and they will be asked to complete the screening visit another time if they would like. Additionally, we may ask participants to provide us with the names and contact information for up to 4 individuals who we can ask to confirm smoking status. We may also perform a cotinine test to verify smoking status. Also, individuals may fill out a MRI safety screening form confirming they are eligible to be scanned for the MRI visit.

Some participants may also be given a camera to use to capture pictures of personalized rewarding objects that are non-smoking (e.g., picture of their pet, favorite book, favorite food) and/or smoking related (e.g., photo of their preferred brand of cigarette, their ash tray, etc). No non-smoking drug related photos will be accepted. Participants may be loaned the camera for a period of approximately 1-3 weeks to capture pictures of rewarding objects. We will instruct participants that the camera is to be used exclusively for capturing pictures for the study and not for personal use. Participants will also be given the option of providing us with relevant photos for the study that they have already taken (e.g., existing photos of their pet, favorite restaurant, etc.) Some participants may not be asked to take their own pictures for the study protocol and may simply be shown neutral or positive pictures/images/objects provided by the experimenters (e.g., shapes, pictures, etc.). Note, no aversive images will be shown to participants. Lastly, subjects may be asked to complete the Personal History Form self-assessment questionnaire on this day on REDCap.

Camera Return Visit:
Participants who were loaned a camera will be asked to come to the lab at Duke to return the camera. The experimenters will ensure that enough pictures have been acquired to use during the experiment.

Participants will be given guidelines about what types of pictures are required for the study. Participants who choose to provide their own images will be asked to upload them to a Duke Box folder and/or to come to the lab and deliver them (e.g., via a thumbdrive).

Participants may also be asked to view and rate the pictures they provide along with neutral and positive images we provide (e.g., puppy, flower) on dimensions such as valence and arousal at this visit and/or the Neurofeedback visit.

Real-Time Neurofeedback Visit:
Eligible participants will be scheduled for an fMRI and/or EEG session to assess and measure the ability to self-activate reward-related regions. The fMRI session will be conducted at either the Duke-UNC Brain Imaging and Analysis Center (BIAC) and/or the UNC Biomedical Research Imaging Center (BRIC), where we have secured a contract for neuroimaging data acquisition. Female participants will have a urine pregnancy test prior to fMRI scanning; the test will be verified to be negative in order to proceed with the scanning session. The EEG sessions will take place in private testing space in the Levine Science Research Center or the BIAC. The real-time neurofeedback visit will be scheduled within 60 days of the screening visit. We are using this window to allow for limited availability of the MRI scanner as well as flexibility to find an ideal time for the participant (e.g., evening or morning scan time). MRI participants may fill out a screening form confirming they are still eligible to be scanned or review a completed screening form if filled out at the screening visit. A carbon monoxide breath test may also be conducted but will not be used in determining eligibility.

Participants may complete some or all of the following tasks: Reward Activation Task, Passive Viewing Task, and Reward Learning Task. All of these tasks aim to assess how adults can learn to interact with neurofeedback provided from an fMRI or EEG system. The tasks vary slightly from each other in terms of stimuli used (personalized pictures, images provided by the experimenters, feedback display, etc.). It may be possible that we will not be able to get a good EEG or fMRI signal for some participants, based on equipment error or head size. If this occurs, participants will be debriefed and paid for their time. We will be sure to emphasize there was no error on the participant's part, and that sometimes the signal is difficult to acquire for a variety of reasons.

Reward Activation Task (ReAcT): Participants may be randomly assigned to one of two groups. One group, the Veridical Feedback Group, will receive veridical neurofeedback from a reward related region, which may include the VTA, striatum, PFC, etc., while they are inside the MRI or while wearing the EEG headset. The other group, the Noise Control Group, will receive noise feedback that they are instructed is real or yoked sham feedback that is yoked to a participant's feedback in the Veridical Feedback Group. This group will serve as a critical control condition for the experiment. All participants will be debriefed in full about the study groups, random assignment, and the purpose of each group in contributing to our understanding of the reward-related brain regions' role in reward processing in individuals with and without ND.

Participants may complete the ReAcT. The ReAcT consists of two types of runs: test runs (one pre-test and one post-test) and training runs (see Fig. 1 for a sample task design). For both groups the pre-test measures baseline reward-related brain activation prior to receiving rt-fMRI or EEG neurofeedback. For

the Veridical Feedback Group, the training runs train participants to use rt-fMRI or EEG neurofeedback to more efficiently and successfully increase their brain activity. For the Noise Control Group, the training runs serve as a control wherein they continue to try to increase brain activity. For all participants, the post-test measures if participants are better able to activate the brain after training.

Test runs: For both Groups the pre and post-test runs are identical and contain two or three trial types: Activate, Count, and Rest. During Activate trials participants will try to increase reward feelings to personalized images of rewarding items (e.g., favorite food, picture of a pet; see Fig. 1). During Count trials participants will count backwards, providing a standardized period for all participants. During Rest trials, participants are instructed to either not think of anything in particular or to view and think about an image shown to them (neutral-positive image). The test runs will have 5-7 repetitions of each trial, separated by a jittered inter-trial-interval (ITI).

Training runs: For both Groups training runs will consist of two or three trial types: Activate, Count, and Rest. Participants will be given the same instructions as the test runs. The Activate and Rest trials will now have an interactive display, e.g., a thermometer, graph, signal bar, etc. Feedback display: For the Veridical Feedback Group, during the Activate trials the feedback display will show the average of brain activity, represented as percent signal change from baseline. The feedback display will be updated approximately every 1-10 seconds. For the Noise Control Group the feedback display will either display random values centered at 0 or yoked feedback from a participant in the Veridical Feedback Group. For both Groups, during the Rest trials, the feedback display will show random values that do not reflect brain activity. The purpose of the rest trial during the training runs will be to serve as a visual control. During Count trials, participants will view a neutral-positive cue or image (e.g., shape or picture). Each trial type will be repeated 5-7 times, separated by a jittered ITI.

Passive Viewing Task: In the passive viewing task participants will view the same images they provide for the ReAcT task. Participants with ND will also view some pictures of personalized smoking cues (e.g., cigarette of their choice). MRI participants who are not ND will not view smoking-related images. Participants will be instructed to relax and passively view the images. They will be asked to rate the images for valence (neutral to positive) and provide intermittent ratings of craving.

Reward Learning Task: In this task, participants will be asked to view various neutral or positive images (symbols/pictures/objects, e.g., white square, yellow circle). Some trials will contain the images only and some will contain the images along with a feedback display. The feedback display may vary somewhat in design and may include feedback designs such as: a thermometer, graph, growing/shrinking balloon, etc. Participants goal will be to learn to interact with the feedback display by regulating their thoughts. As part of this interaction with the feedback display, participants will rate their level of motivation prior to, during, and/or after each feedback trial.

Delay to Smoking Assessment: for ND individuals, we may assess time (in minutes) that participants take to smoke their first cigarette (time and space permitting). After the MRI and/or EEG sessions we may give participants the opportunity to smoke a cigarette(s) if they would like. If we do the assessment, we will measure both the time it takes for them to take their smoking break as well as the number of cigarettes smoked. We may additionally collect self-report measures of craving.

Stimuli:
ReAcT Task: for the Activate trials in the ReAcT task, participants will be asked to provide approximately 50 pictures of personally rewarding objects or environments from their lives (e.g., family members, pets, favorite foods, favorite books, favorite places etc.). Participants will be asked to give the experimenter these electronic images (via the loaned camera or another method of their choice, e.g., thumbdrive) at least a few days prior to the fMRI session so that the experimenter can program them into the task. By doing so, the experimental task is personalized for each participant whereby they view their own personally rewarding images while they are inside the MRI machine or wearing the EEG headset. We believe this will elicit a much more realistic assessment of participant's reward sensitivity relative to generic images of rewarding items. These images will be stored on a secure server at Duke University. They will labeled according to the de-identified participant number and will not be linked to any PHI. For the Count and Rest trials in the ReAcT task we will provide generic neutral and positive stimuli as control images.

Passive Viewing Task: In the passive viewing task participants will view the same images they provide for the ReAcT task. Adults who smoke will also view pictures of personalized smoking cues (e.g., cigarette of their choice, favorite place to smoke, etc.).

Reward Learning Task: in this task participants will view various neutral or positive images including shapes, objects, scenes, etc.

Collection of psychophysiological data: In conjunction with fMRI data collection, physiological measures of heart rate and respiration may be recorded using an MR-safe commercial system (e.g., BIOPAC systems, Goleta, CA or the built-in GE equipment) to permit removal of physiological noise from the fMRI signal. This equipment is MR safe and has been used extensively at BIAC. Heart rate and respiration data will not be collected when using the EEG headset. Eye tracking data may also be collected. We may use the Tobii Pro eye tracker X2-60 (https://www.tobiipro.com/product-listing/tobii-pro-x2-60/), which is a screen-based eye tracker that sits on the computer. This eye tracker is not placed on the participant and therefore causes no physical discomfort and minimal disruption to the participant.

Questionnaire measures: The following self-assessment questionnaires may be completed at the Screening Visit. Note, the smoking related measures will only be collected for the smokers. Personal History Form, Personalized smoking history questionnaire, the Fagerström Test of Nicotine Dependence (FTND; 7 item), Center for Epidemiologic Studies Depression (CES-D; 20 item), the Temporal Experience of Pleasure Scale (18 item), Questionnaire of Smoking Urges-Brief (5 item), Contemplation Ladder (1 item), MNWS (8 item), SDSS (23 item), WISDM (37-item), Other tobacco use questionnaire (2 item), MTQ short form (48 item), the Snaith-Hamilton Pleasure Scale (SHAPS; 14 item), the Daily Experiences of Wanting and Liking (DEWL; 31 item), the General Self-Efficacy Scale (10 item), and the Multidimensional Personality Questionnaire Brief (MPQ; 155 items). We estimate that completion of these questionnaires will take approximately 45-60 minutes.

The following self-assessment questionnaires may be completed during the MRI or EEG Visit. Note, the smoking related measures will only be collected for the smokers. The Positive Affect Negative Affect

Scale (20 item), the SHAPS, the DEWL, the BVAQ English Questionnaire (40 item), Personal History Form, CES-D, Difficulties in Emotion Regulation Scale (36 item), the General Self-Efficacy Scale, the Fraser Imagery Questionnaire (10 item), the Spontaneous Use of Imagery Scale (12 item), and the State and/or Trait Anxiety Inventories (20 items each) will index state and trait personality measures. We may additionally collect the following smoking-related measures: the Wisconsin Smoking Withdrawal Scale (28 item), the MNWS (may be administered pre and post neurofeedback session), Contemplation Ladder, the Questionnaire of Smoking Urges58 (may be administered pre and post the neurofeedback session). We estimate that completion of these questionnaires will take approximately 35 minutes.

Self-report: participants will be asked to self-report strategies they used to regulate their brain activation. They may be asked to write them down or record them using software such as Audacity (see Pre-Session Questionnaire, Post-Session Questionnaire, and SB Post Session Questionnaire Final as examples). Participants may also be asked to rate their levels of motivation, arousal, enthusiasm, etc. throughout the experiment via making responses on a button box or response dial.

Smoking biomarker: To verify smoking status for nicotine dependent participants, we will measure expired air CO via a handheld monitor (e.g., Vitalograph). To ensure recency of smoking that is sufficient to produce detectable levels of CO, participants with CO levels below the required cutoff will be permitted to smoke one of their own cigarettes outside the lab prior to providing a second breath sample if they choose to do so.

Genetic measures: Saliva may be collected. If so, we will use a commercially available kit from Oragene (http://www.dnagenotek.com/ROW/products/OG500.html). This is a very simple procedure in which participants deposit saliva into a plastic tub. It is non-invasive and takes a few minutes. The tubes will be de-identified and labeled by participant ID number. They will be stored in a locked cabinet inside secure office space. These saliva samples are stable stored at room temperature and can be kept in room temperature storage for up to 5 years. Once data collection is complete, we will send them to the Duke University DNA Analysis Facility for one time analysis. We will examine genetic markers related to dopamine function. Examples include both SNPs (e.g., DRD1, DRD2) and VNTRs (e.g., DAT, MAOA).

Follow-up Phone Call/Debriefing:
For ND individuals: participants may be called and/or sent a link to a REDCap survey 1 day, 1 week, and/or 1 month following the MRI visit to assess if there is any change in their smoking behavior following study participation. We will ask participants if they have modified their smoking behavior in any way (e.g., # of cigarettes smoked, craving, etc, see Contemplation ladder and rtNic.01 Follow up Questionnaire as examples). During the last phone call, we will debrief participants regarding which group they were in (Veridical Feedback Group or Noise Control Group) and answer any remaining questions they have about the study.

Selection of Subjects

List inclusion/exclusion criteria and how subjects will be identified.
Inclusion Criteria:
18-55 years of age

In good general health
Male or Female
For ND individuals: Self-reported smoking ≥ 5 combustible cigarettes per day
For ND individuals: Afternoon expired CO concentration of ≥ 8 ppm
For ND individuals: Is willing and able to abstain from smoking for a few hours

Exclusion Criteria:
Current chronic/significant medical condition
Current or past 6 month use of prescription medications for psychiatric conditions (e.g., depression, anxiety)
Current or past 6 month diagnosis of anxiety, bipolar disorder, depression, OCD, schizophrenia, psychosis, or personality disorder.
Current substance abuse or dependence or history within the last 6 months (other than nicotine for ND individuals)
For ND individuals: Currently on nicotine replacement therapy
For ND individuals: Individuals who role their own cigarettes
For MRI subjects: Positive drug test for anything other than marijuana
For MRI subjects: Daily cannabis use
For MRI subjects: Consume more than 21 alcoholic drinks per week
For MRI subjects: Use harder drugs (e.g., cocaine, methamphetamine) more than 10 times per year
For MRI subjects: Currently taking medication that directly acts on the dopamine system (e.g., L-DOPA). We will record a list of all medications they are currently on and assess if they affect the dopamine system. If so, they will be excluded.
For MRI subjects: Claustrophobia or other contraindications to MRI scanning
For MRI subjects: If female, pregnancy as determined by urine pregnancy test on the day of MRI scanning
For MRI subjects: Presence of any metal in the body (e.g., implant, non-removable piercing, metal IUD)
For MRI subjects: Head injury resulting in loss of consciousness
For MRI subjects: Worked with metal (e.g., welding) or had an injury to the eye involving metal
For MRI subjects: If they weigh more than 200 pounds, the PIs will make their best judgement based on other factors including participant height and prior experience in with MRI scans
Inability to understand written and/or spoken English language
Any other participant characteristic, history, and/or behavior that in the opinion of the investigator would contraindicate participation in the study.
Subject Recruitment and Compensation
Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.
Research participants will be recruited from the Duke University community and surrounding Durham area via flyers posted in public places, print advertisements in local publications, advertisements online (e.g., Facebook, Reddit, Craigslist, DukeList) and word of mouth. To qualify for the study, participants who smoke must self-report smoking greater than or equal to 5 cigarettes per day, but otherwise be in

good health (see criteria above). Non-smokers must be in good health (see criteria above). They can and may be members of the Duke community (i.e., either students or employees).

Participants will be compensated $35/hour for behavioral portions of the proposed studies (e.g., screening visit, camera return visit, follow-up phone calls and portions of the MRI session that occur outside of the MRI), and $50/hour when they are inside the MRI machine. When applicable, participants will receive a $20 bonus for taking and/or providing good quality pictures (if needed for the experiment). Participants will receive payment via cash or check for their participation at the end of the study.

Risk/Benefit Assessment

Only eligible participants as defined by the protocol will be enrolled in the study. Pregnant women, or prisoners will not be enrolled in this study. No direct benefits are expected. Knowledge obtained from this study may benefit other adults with or without nicotine dependence in the future.

Questionnaires: It is possible that participants can experience frustration from performing the tasks or the questions being asked will make them uncomfortable. Participants may refuse to answer any of the questions and may take a break at any time during the study. Participants may also stop participation in this study at any time.

Confidentiality: There is the potential risk of loss of confidentiality. Every effort will be made to keep participant information confidential, however, this cannot be guaranteed.

fMRI: Although there are no known long-term health risks associated with the magnetic fields and radiofrequency energy used to make MR images, safety and comfort issues impose restrictions upon who can be scanned. For example, participants who have implanted medical devices, such as pacemakers, cannot be safely scanned, nor can participants who have shrapnel or metal debris within their bodies. Although pregnancy is not considered a contraindication to clinical MRI scanning and no studies have demonstrated that MRI is harmful to a fetus, Duke IRB regulations specifically exclude pregnant women from research scanning. Participants who are too large (>250lbs) may not fit comfortably in the scanner bore, and participants who feel anxious in confined spaces may not tolerate a research scan. In order to protect participants against potential risks of participating in MRI research, all participants indicating interest in participating in MRI research complete a preliminary phone or email screening to eliminate from participation those who cannot be safely scanned.

EEG: We will use the Emotiv EPOC+ wearable EEG headset (https://www.emotiv.com/epoc/). This device is noninvasive and sits comfortably around the participant's head. It is a wireless EEG headset making it more portable and comfortable than a traditional EEG setup. There are no long-term health risks associated with EEG. One possible discomfort is minor skin irritation or redness. It is also possible that the headset may be uncomfortable for some participants to wear (e.g., result in a headache). Participants may take a break or stop participation at any time.

Anxiety assessment procedure

Some participants may feel uncomfortable or confined once positioned within the bore of the MRI system. This potential reaction is reduced by discussing the procedure prior to entry into the magnet room, by providing the participant with a panic button that they can use to immediately signal the experimenter and the MR technician, and by frequently communicating with the participant over the intercom during the scan session. In addition, participants may be placed into a practice mock scanner prior to the regular scanning session, in order to determine if they will be comfortable in the MRI. This mock scanner consists of a decommissioned GE scanner bore without active RF gradients. This facility is located adjacent to the research scanners at the BIAC. Nevertheless, if participants continue to feel uncomfortable, the imaging procedure is terminated and the participant is removed from the magnet. Special protections will also be implemented to prevent claustrophobia or panic attacks during the neuroimaging session. A contingency plan has been established by Dr. Adcock and her team and is designed to minimize anxiety. The procedure is detailed below:

Experimenter: I'd like to ask you some questions to see how you're feeling right now. On a scale of 1 to 10, where 1 is no anxiety, and 10 is the most anxiety you have ever felt, how anxious do you feel right now?

Anxiety Rating: _____

If the Anxiety rating is 7 or higher: Do you feel like you are in control of your anxiety right now, or do you feel like you may lose control of your anxiety?

In control? YES | NO

If the anxiety rating is 7 or higher AND the participant reports feeling out of control, implement Panic Protocol, below.

If the anxiety rating is 5 or higher, implement Relaxation Protocol, below.

If the anxiety rating is 4 or lower, offer the Relaxation Protocol, below.

Panic Protocol

Experimenter: Let's take a walk for a few minutes.

Escort the participant from the experimental area, ideally to a comfortable area where windows and/or exits to the outside of the building are visible. (NOTE: if the participant is unwilling to walk with the experimenter, proceed to deep breathing, below.) You don't need to take the most direct route to your destination: physical activity such as walking will help to reduce the participant's anxiety. Try to make small talk with the participant as you walk, with the goal of distracting the participant from his/her symptoms of anxiety. After walking for a few minutes, invite the participant to sit down and query current anxiety using the two questions from the Assessment section, above. Anxiety Rating: _____

In control? YES | NO

If the participant's anxiety has reduced and they are no longer feeling out of control, proceed to the Relaxation Protocol, below. If not:

Experimenter: Okay, I would like us to try some deep breathing exercises to help reduce your anxiety. Place your hand on your abdomen right below your ribcage, like this. Experimenter should demonstrate this and all steps in the relaxation breathing protocol. Now, inhale slowly and deeply through your nose into the "bottom" of your lungs – in other words, send the breath down as low as you can. You should feel the hand on your abdomen rise with your breath. Your chest should only move a little bit.

After you take in a full breath, pause for a moment and then exhale slowly through your nose. (If they have a cold or for some other reason nose breathing is difficult, it's OK if they breathe through their mouths.) Exhale fully. As you exhale, allow your whole body to just let go.
Take a few more breaths like this.
We are going to do ten breaths like this. Try to keep your breathing smooth and regular, without gulping a big breath in or letting your breath out all at once. See if you can count to four on each inhale, and count to four on each exhale. Remember to pause briefly at the end of each inhalation. Count from ten down to one on each exhalation. If you find yourself getting light-headed, let me know and we'll stop and breathe normally for a while. So do it with me.
Slow inhale … Pause … Slow exhale: Count ten
Slow inhale … Pause … Slow exhale: Count nine
Etc., down to one.
Query current anxiety using the two questions from the Assessment section, above.
Anxiety Rating: _____
In control? YES | NO
If anxiety rating is still 7 or higher, do another round of 10 breaths of deep breathing and reassess anxiety. If anxiety rating has not reduced after that, escort the participant to the Duke Emergency Department.
If anxiety rating is reduced and participant is reporting an increasing sense of control over his/her anxiety, proceed to the Relaxation Protocol, below.
Relaxation Protocol
Escort the participant to a room outside the testing environment where a comfortable chair is available. Ask the participant to sit down, and say,
I would like you to listen to this tape and follow the instructions. It will be guiding you through some relaxation exercises. It will take approximately ten minutes to complete the tape. I'll come back to check on you when you're done. Start the progressive muscle relaxation tape. When the tape is finished, assess the participant's anxiety level a final time.
Anxiety Rating: _____
In control? YES | NO
Provide professional referral resources as needed.

Dr. Alison Adcock who is psychiatrist will be on call during all scanning sessions.

Adverse Event and Serious Adverse Event reporting: Adverse events are recorded in an Adverse Event Log and reported annually to the IRB via the Continuing Renewal Process. In Accord with the IRB, AEs are considered SAEs, if they are serious, unexpected, and related to the protocol. We will report SAEs to the IRB within 1 week of occurrence.

Data Analysis & Statistical Considerations

Behavioral, EEG, and genetic data will be analyzed using statistical software including MATLAB, R, Python, and SPSS. The genetic information will be sent to the Duke University DNA Analysis Center for analysis. Imaging data will be analyzed using commercially available programs including Python, MATLAB, and FSL.

For the fMRI data, following data collection, the time series of activation within the VTA107,125 will be extracted for each participant. Primary analyses on these data will be conducted on a within and between-subject basis as follows:

To assess the ability of adults with and without ND to activate reward-related brain areas (e.g., VTA, striatum, PFC). To address this question we will extract time courses from the target areas and examine the brain response (BOLD signal) to personalized and non-personalized drug and non-drug cues.
To evaluate whether rt-fMRI neurofeedback improves the ability to increase reward-related brain activation in individuals with and without ND. To address this question we will compare individual's BOLD response to: baseline (passive viewing of reward images), Pre-Test (view personalized and non-personalized non-drug cues prior to neurofeedback), Training (view personalized, non-drug cues while receiving neurofeedback), and Post-Test (view personalized and non-personalized non-drug cues following neurofeedback). In this manner we will characterize and quantify individual's ability to increase brain activity to personalized, non-drug rewarding stimuli.

To examine the relationship between activation of reward-related regions via neurofeedback and dopamine availability (as assessed genetically). To assess this question we will first send the genetic data to the Duke University DNA Analysis Facility for analysis. Once the SNPs and VNTRs have been analyzed we will correlate individual's level of dopaminergic related genetic material (e.g., COMT, DAT) to their ability to regulate reward-related activation during the task.

To examine the effects of neurofeedback on clinically relevant outcomes, including reward responsivity and smoking related behaviors. To assess this we will examine participants brain activity during the Passive Viewing Task and the ReAcT. We will also perform a simple Delay to Smoking Assessment where we will measure (in minutes) how long participants take to smoke their first cigarette. We will also measure how many cigarettes they smoke during their break. We will correlate individual's ability to increase brain activation to personalized, non-drug cues in the ReAcT with both their time to initiate smoking and the number of cigarettes smoked.

Data & Safety Monitoring

Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).
Only participants meeting all inclusion and no exclusion criteria will be enrolled in the study. Pre-screening for appropriateness to undergo MRI scanning will be completed prior to the procedure to make sure to exclude participants who are not safe to undergo MRI scanning such as people who have metal implants, non-removable piercings, a copper IUD, have worked with metal, or had an eye injury involving metal. Protocols are in place for participants who may experience anxiety or panic attacks during study assessments. Urine pregnancy test is required for each female prior to scanning procedure. The test must be negative in order to proceed. The PI and her study team will review appropriateness of participants for the study.