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Effects of transdermal nicotine on response inhibition to emotional cues in schizophrenia

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Table of Contents:

1 Background 4
2 Rationale and specific aims 4
3 Animal studies and previous human studies 6
3.1 Animal studies 6
3.2 Human studies 6
4 Inclusion/exclusion criteria 7
4.1 Inclusion criteria for schizophrenia subjects 7
4.2 Exclusion criteria for schizophrenia subjects 8
4.3 Inclusion criteria for healthy controls 8
4.4 Exclusion criteria for healthy controls 8
5 Enrollment/randomization 9
5.1 Subject recruitment and enrollment 9
5.2 Process of consent 9
5.3 Evaluation of subject capacity to provide informed consent 10
5.4 Randomization 10
6 Study Procedures 10
6.1 Baseline: day 0 10
6.2 Testing: days 1 and 2 11
7 Study drug 12
7.1 Background 13
7.2 Drug source 13
7.3 Storage, preparation and use 13
7.4 Justification for the use of placebo 13
8 Risks, minimizing risks, and potential benefits 13
8.1 Risks 13
8.1.1 Study medication: transdermal nicotine 13
8.1.2 Psychological assessments and Emotional Go/NoGo task 14
8.1.3 Electroencephalography (EEG) 15
8.2 Minimizing Risks 15
8.2.1 Risk of study medication 15
8.2.2 Risk of psychological assessments and Emotional Go/NoGo task 15
8.2.3 Electroencephalography (EEG) 15
8.2.4 Risk of breach of data security and privacy 15
8.2.5 Subject Monitoring and Emergency Procedures 16
8.3 Potential benefits 16
9 Research alternatives and economic considerations 16
9.1 Alternatives to participation in the study 16
9.2 Payments for participation 16
9.3 Costs for participation 17
9.4 Medical treatment in case of injury 17
10 Reporting of adverse events or unanticipated problems involving risk to participants or others 17
10.1 Greater than minimal risk Data and Safety Monitoring Plan 17
10.1.1 Personnel responsible for the safety review and its frequency 18
10.1.2 Attribution of adverse events 18
10.1.3 Plan for grading adverse events 18
10.1.4 Plan for determining seriousness of adverse events 18
10.1.5 Plan for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs, including Adverse Events) to the IRB 19

10.1.6 Plan for reporting adverse events to co-investigators on the study, DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies. 19
11 Study withdrawal/discontinuation....20
12 Statistical considerations 20
12.1 Power analysis 20
12.2 Data analysis plan 21
12.3 Inclusion of men and women 21
13 Privacy/confidentiality issues....21
14 Follow-up and record retention 21

1 Background

Aggressive behavior can be largely divided into either instrumental aggression, which is purposeful aggression to obtain a desired outcome, or impulsive aggression, which is sudden, inappropriate aggression mounted in the context of strong emotion such as anger or frustration.[1] Impulsive aggression frequently complicates severe neuropsychiatric disorders occurring across the lifespan, worsens outcomes,[2] and isolates patients from their communities. Management of persistent impulsive aggression is an unmet challenge for diverse healthcare settings such as residential and nursing treatment facilities, civil and forensic psychiatric hospitals, and criminal justice settings.[3, 4] For example, while the majority of people with schizophrenia spectrum disorders are not violent, such conditions confer an aggregate increased risk of violence and aggression,[5-7] with more than half of patients in forensic psychiatric settings diagnosed with schizophrenia.[8] In recent decades, such patients have increasingly been institutionalized in prisons and jails[9] at a cost of more than $14 billion,[10] yet still receive substandard care[11] and have high rates of reincarceration.[10] Vast expenditures to treat aggression also occur in non-correctional settings. For example, one-third of the total $236 billion cost to treat Alzheimer's disease in the U.S. is spent to manage behavioral and psychological symptoms, including aggression.[12, 13] Current treatment approaches for aggression in neuropsychiatric disorders incorporate environmental, behavioral, and pharmacological interventions,[4] yet aggressive behaviors commonly remain treatment-resistant.[3, 14-16] For these patients, psychopharmacological agents with diverse pharmacological actions are trialed off-label, despite limited pathophysiological rationale, inconsistent clinical benefit,[5, 17] and increased morbidity or mortality.[18] To address this growing need with important individual and societal implications, novel therapeutic approaches must be designed based on an increased understanding of the neural circuits governing aggressive behavior.

2 Rationale and specific aims

This human laboratory study seeks to test the hypothesis that activation of nicotinic acetylcholine receptors (nAChRs) in the brain will reduce impulsive behavior in response to negative emotional cues as compared to neutral emotional cues. Because impulsive action during negative mood states is strongly correlated with impulsive aggression in both healthy individuals and individuals with schizophrenia (discussed below), our overarching, long-term goal is to determine whether nAChRs in general as well as specific nAChR subclasses might represent novel treatment targets to reduce impulsive aggressive behavior, a significant public health problem.

Nicotinic acetylcholine receptors are a large family of excitatory, pentameric, ionotropic, ligand-gated ion channels located throughout the brain and the remainder of the body. Their endogenous ligand is acetylcholine, yet this family is defined by their common activation by nicotine. Interestingly, anti-aggressive, or "serenic" effects of nicotine have been demonstrated across a number of animal models, including mice, rats, and non-human primates,[19] and multiple human laboratory studies demonstrate an anti-aggressive effect of nicotine in humans.[20-22] As detailed in section 3.1, our laboratory has also demonstrated that acute administration of nicotine at relatively low doses results in reduction of aggressive behaviors in mouse models.[23, 24] Because nicotine is active at all nAChRs, we explored this mechanism further and found that hippocampal alpha-7 nAChRs were both necessary and sufficient for nicotine's serenic effect.[23, 24] Consistent with these findings, there is substantial evidence in humans that reduction of alpha-7 nAChR signaling enhances aggressive behavior,[25] including in individuals with 15q13.3

microdeletion syndrome, a genetic disorder resulting from the deletion of the region of chromosome 15 containing the gene coding for alpha-7 nAChRs.[26, 27] We have also translated these findings into human clinical populations. We recently demonstrated the safety and efficacy of transdermal nicotine to reduce aggression and irritability in young adults with autism spectrum disorder,[28] described in section 3.2. This work, along with other previous case studies in humans,[29-31] supports targeting nAChRs using transdermal nicotine to reduce aggressive behaviors.

Urgency is a behavioral construct defined as the tendency to act rashly in the context of strong positive or negative emotion,[32] and explains a large degree of variance in the development of impulsive aggression in subjects with schizophrenia[33] and other populations without psychiatric disorders.[34] In patients with schizophrenia, degree of urgency correlates with structural and functional changes in a neuronal network involving prefrontal cortical and limbic/cognitive control brain regions.[33] A number of previous studies have similarly demonstrated impulsivity in the context of negative emotion, called "negative urgency", correlates with history of aggression,[35, 36] as well as substance use and other risky behaviors [37]. Urgency is a hereditable trait[38] that may be considered an endophenotype of impulsive aggression.[39]

Recent studies in humans have explored the relationship between mood-related impulsivity (i.e. urgency) and aggressive behavior using an *Emotional Go/NoGo* task. This task measures responding or response withholding to visual stimuli of neutral or emotional (typically negative) valence, and quantifies reaction time and commission/omission errors as a function of stimulus valence. Using an Emotional Go/NoGo task, Krakowski et al. studied healthy controls, patients with schizophrenia with or without a history of violence, and non-psychotic individuals with history of violence.[36] In all groups, emotional valence had a significant effect on error commission. In schizophrenia patients, individuals with history of violence were significantly faster to make an incorrect response to negative stimuli (i.e. not withhold a response) than patients without history of violence, whereas the two groups did not differ in response times to neutral valence stimuli. Other studies have also demonstrated an interaction between emotional valence and impulsive errors in schizophrenia,[40] as well as a relationship between emotional valence, impulsive errors, history of violence, and frontal cortex 5-HT1B receptor binding.[41]

While our studies in mice suggest a direct effect of nAChR stimulation on aggression through activation of the alpha-7 nAChR[23, 24] and are supported by our results using transdermal nicotine in humans,[28, 31] to our knowledge no previous studies have directly examined the relationship between pharmacological targeting of nAChRs using transdermal nicotine and effects on impulsivity in the context of emotional cues in humans. W**e now aim to directly test this hypothesis using an Emotional Go/NoGo task in subjects with schizophrenia and healthy controls to determine whether transdermal nicotine improves impulsive behavior and neural correlates in the context of negative and neutral valence cues.** Given the relationship between impulsivity and aggressive behavior, the findings of this proposed study will strongly inform future studies of targeting nAChRs broadly and alpha-7 nAChRs more specifically to identify novel treatments for individuals with severe neuropsychiatric disorders struggling with persistent pathological impulsive aggression.

3 Animal studies and previous human studies

3.1 Animal studies

There exists an extensive literature on the effects of nicotine on animal behavior. As noted above, nicotine has a substantial evidence base suggesting it may have specific serenic effects, i.e. the ability to reduce aggressive behavior (reviewed in 42). Our laboratory has performed several lines of studies aimed at understanding how nAChRs, in particular alpha-7 nAChRs, regulate aggressive and related behaviors in mice.[23, 43] We first replicated previous studies demonstrating a dose-dependent reduction in aggressive behavior by intraperitoneal administration of nicotine. We then found that blockade of alpha-7 nAChRs, but not beta-2-containing nAChRs, blocked the serenic effects of nicotine, implicating a specific role for alpha-7 nAChRs in nicotine's serenic effects. We also found that specific agonism of alpha-7 nAChRs through the alpha-7 nAChR partial agonist GTS-21 recapitulated nicotine's serenic effects. Consistent with alpha-7 nAChRs localization on GABAergic inhibitory interneurons in the dentate gyrus of the hippocampus, we found that GTS-21 reduces activation of the dentate gyrus, and that knockdown of alpha-7 nAChRs reduces GTS-21's serenic effect.[24] These findings suggest that nicotine exerts its effect, at least in part, via hippocampal inhibition thorugh alpha-7 nAChR signaling, consistent with findings from human neuroimaging studies.[44]

Effects of nicotine and nAChR stimulation on impulsivity in rodents have also been studied, in part inspired by the relationship between higher levels of smoking in individuals with neuropsychiatric disorders demonstrating poor impulsive control, such as attention deficit hyperactivity disorder (ADHD) and schizophrenia.[45] Mice performing an operant task that measured premature and signaled nose pokes and performance efficiency found that acute administration of nicotine improved performance efficiency, however chronic nicotine and nicotine withdrawal did not affect performance efficiency.[46] However, interestingly forms of motor of choice impulsivity do not rely on beta-2-contaning nAChRs.[47] Mice with genetic deletion of the alpha-7 nAChR demonstrate increased impulsivity compared to wildtype mice in the five-choice serial reaction time task,[48] whereas no other nAChR knockout mouse line demonstrated changes on this task. Interestingly, encenicline (EVP-6124), also an alpha-7 nAchR partial agonist, demonstrated improvements in impulsive action in rats in the 5 choice-continuous performance task.[49] These findings support the relationship between the alpha-7 nAChR and regulation of impulsivity, as well as the potential to improve impulsive responding through its pharmacological targeting by nicotine.

3.2 Human studies

While the effects of nicotine on response inhibition to emotional cues are unknown, previous studies of acutely administered nicotine in humans have shown effects on closely related behavioral constructs and effects on hippocampal inhibition, which we believe is mechanistically important for nicotine's serenic effects.[43] Transdermal nicotine improves performance on the Continuous Performance Test Identical Pairs (CPT-IP) Version in both healthy controls and non-smoking patients with schizophrenia, with improvements to a greater extent in the schizophrenia patients.[50] These findings extend previous work demonstrating positive effects on attention in patients with schizophrenia of acutely administered nicotine.[51, 52] Clinical trials and case series have demonstrated effects of nicotine on reduction of agitation and aggression in subjects with schizophrenia presenting to an emergency department[53] and in elderly subjects with severe dementia.[29, 30] Nicotine was also shown in subjects experiencing nicotine

withdrawal to return provoked aggression in a laboratory paradigm back to baseline levels.[22]

Multiple lines of evidence suggest that pan-activation of nAChRs by nicotine, and more selective activation of alpha-7 nAChRs may influence aggression and related behaviors through effects on regulatory circuitry of affect. For instance, an open label study of transdermal nicotine recently demonstrated substantially improvement in mood symptoms in a population of older adults with late-life depression,[54] in agreement with multiple previous studies reporting improvement in mood symptoms by transdermal nicotine.[55-57] Our group also found in a secondary analysis of data from a randomized, double blind, placebo controlled study of GTS-21 in patients with schizophrenia that GTS-21 exerts a specific beneficial effect on affect and mood, as measured by the Brief Psychiatric Rating Scale.[58]

Several studies have explored the effects of acute administration of nicotine and selective alpha-7 nAChR agonists on brain activity in regions important for cognition, impulsivity, and aggression.[59] For example, acute administration of transdermal nicotine, 7 mg, in subjects with schizophrenia restored connectivity in the ventral attention network during a go/no-go task with environmental noise distractors,[60] as well as modulated neuronal responses in several brain regions during an auditory selective attention task with environmental noise distractors.[61] An alpha-7 partial agonist was also shown to reduce hippocampal hyperexcitability during a smooth pursuit eye movement task in subjects with schizophrenia,[44] as well as influence default mode network activity in schizophrenia.[62] Positron Emission Tomography (PET) studies also interestingly demonstrated an interaction between trait hostility and brain metabolism in smokers and non-smokers administered acute nicotine by transdermal patch performing a provoked aggression task.[63, 64]

Taken together, previous investigation suggests that acute administration of nicotine in subjects with schizophrenia can influence cognitive processes related to impulsivity and aggression, and target neural substrates overlapping with key brain regions for aggression and impulsivity identified from mouse models. These studies provide strong rationale to directly test the effects of nicotine on response inhibition to emotional cues, which would provide strong evidence to support targeting nAChRs for aggression and related behaviors in clinical populations.

4 Inclusion/exclusion criteria

4.1 Inclusion criteria for schizophrenia subjects

1. Men and women age 18 - 65.
2. Communicative in English.
3. Provide voluntary, written informed consent.
4. Physically healthy by medical history,and ECG examination.
5. BMI $\geq$ 17.5 and $\leq$ 45.
6. Diagnosis of schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) confirmed by Structured Clinical Interview for DSM-V (SCID) or diagnostic interview with a trained clinician.
7. Stable medication regimen over at least the past two weeks, including the use of either an oral or intramuscular administration of an antipsychotic medication. Additionally, subjects may take any prescribed medication aside from a nicotine-

containing product as long as it has been regularly taken over the past two weeks, including as-needed ("PRN") medication.
8. Negative urine toxicology and negative urinary cotinine (to confirm no recent nicotine use) at screening.
9. Does not meet criteria for substance or alcohol use disorder per the SCID over the past 6 months
10. For females, no longer of child-bearing potential, or agreeing to practice effective contraception during the study (e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine system [IUS]; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository; male partner sterilization; or true abstinence when this is in line with the preferred and usual lifestyle of the subject); and,
11. For females of child-bearing potential, must have negative urine pregnancy test at time of screening visit and before each testing day.
12. Not breastfeeding/nursing at time of screening or at any time during the study.

4.2 Exclusion criteria for schizophrenia subjects

1. Age less than 18 or greater than 65.
2. Not communicative in English.
3. Unable to provide written informed consent.
4. Active suicidal ideation or suicidal behavior.
5. Current, unstable medical or neurological illness or significant abnormality on ECG.
6. History of severe head trauma.
7. BMI < 17.5 or > 45.
8. History of allergy to transdermal patches.
9. Screening visit resting heart rate > 110 or < 50 beats per minute, or known history of clinically significant cardiac rhythm abnormalities.
10. Screening visit systolic blood pressure > 160 or < 90, or diastolic blood pressure > 95 or < 50.
11. Positive urine toxicology or positive urine cotinine during screening.
12. Meets criteria for diagnosis of substance or alcohol use disorder by SCID within the past 6 months.
13. Reports any tobacco smoking or nicotine use over the past month.
14. Not taking an antipsychotic medication.
15. Positive urine pregnancy test at time of screening, before each testing day, or any potential concern for pregnancy at any time during the study
16. Breastfeeding/nursing at time of screening or at any time during the study.

4.3 Inclusion criteria for healthy controls

All of the above except for subjects will be psychiatrically healthy and not taking psychotropic or potentially psychoactive prescription medication.

4.4 Exclusion criteria for healthy controls

All of the above and in addition:

1. Current use of psychotropic or potentially psychoactive prescription medication.
2. Major psychiatric disorder as determined by DSM-5 (schizophrenia, major depression, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, etc.)

5 Enrollment/randomization

5.1 Subject recruitment and enrollment

The research team will identify potential subjects by morning reports at the Psychotic Disorders Research Program at the Vanderbilt Psychiatric Hospital and other IRB approved screening information, and/or by review of provider's caseloads at Vanderbilt using eStar/EPIC. Potential subjects may also be identified by broadly targeted advertisements with IRB approval. Patient information will be reviewed only for the purposes of determining possible eligibility for the study. All screening information obtained during these reviews will be documented on a screening form or in a password-protected database. Screening databases will include inclusion/exclusion information, as well as the patient's name, medical record number, appointment times/dates (for outpatients), and the name of the clinical care provider. All identifying information, such as name, medical record number, and contact information, will be stored in a password-protected database. These databases and subject screening forms will be kept for internal monitoring purposes only (i.e., tracking of primary reasons for exclusion from the study). When adult patients (ages 18 to 65) are recruited directly from a mental health clinic or hospital, the subject's clinical care provider will first determine whether or not it is appropriate for us to invite the subject for participation in the study, and the subject must agree to being approached. Adolescent patients (13-17 years old) will not be recruited for this study. Advertising materials may be distributed to physicians' offices and outpatient clinic waiting rooms for the purpose of informing the patient and clinical care providers about the study, but providers who are not part of our study staff will not be asked to describe any part of the study to the patient. Providers will only be asked to inquire about the patient's interest in hearing about research in general. Providers may be contacted by study staff through email, phone, secure EPIC messaging, face-to-face, or by flagging patient charts through front desk staff or inpatient unit staff. Information will not be provided to front desk staff or inpatient unit staff regarding which study the patient is being considered for. We will only recruit patients who are stable. Patients who initiate contact with study personnel in response to an advertisement or flyer will be carefully prescreened and have a thorough clinical evaluation by the study doctor, study coordinator, or study personnel to determine stability of mood and medication. Patient information contained in subject databases may be used to telephone potential subjects. These databases will be comprised of subjects who have given prior consent to be contacted by various researchers about participation in research.

5.2 Process of consent

Consent will be obtained from participants in a private office at the VPH on the screening visit. The subject and one of the investigators will necessarily be present for the consent process. Participants who are accompanied by a family member or caregiver will be allowed the option of having that person in the room if desired. The inclusion and exclusion criteria will ensure that participants have capacity for informed consent (see below). Participants will be given ample time to ask questions during the consent procedure, and to consult family members or caregivers prior to making a decision if they so wish. Participants will be informed during the initial telephonic contact that they will be monetarily compensated for this initial visit whether or not they decide to participate in the study.

5.3 Evaluation of subject capacity to provide informed consent

During the screening process, the details of the study will be explained carefully to the subject. After time has been permitted for the participant to ask any clarifying questions, the subject will be asked to summarize their understanding of the procedures, risks and benefits of the study using a "talk back" method. The study personnel will address any inaccuracies, but after two attempts at clarification, if a subject is unable to give a reasonable account of the study procedures, risks and benefits, they will be considered to not have capacity for consent. As a board-certified psychiatrist, Dr. Lewis has extensive experience in capacity evaluations of individuals with psychiatric disorders, and will ensure research staff is trained to appropriately determine capacity to consent to the research study.

5.4 Randomization

Treatment order will be block randomized by a member of the Center for Cognitive Medicine within the Department of Psychiatry at VUMC who is not otherwise involved in this study. All investigators and subjects will be blinded to treatment order.

6 Study Procedures

All study procedures will take place at the Vanderbilt Psychiatric Hospital. We will recruit clinically stable outpatient adult men and women with schizophrenia or schizoaffective disorder, age 18-65, with similar clinical characteristics to those described in a previous clinical study of acute transdermal nicotine administration in subjects with schizophrenia and healthy controls.[61] Inclusion and exclusion criteria are listed above in section 4. All participants will provide written informed consent. This study population, including non-smoking patients with schizophrenia, has been consistently successfully recruited for imaging studies in the lab of Dr. Stephan Heckers, in the quantities necessary for the current project.

6.1 Baseline: day 0

Subjects completing a telephone or other initial screen will be invited to complete a baseline screening day in person. At this visit, a primary diagnosis of schizophrenia or schizoaffective disorder will be confirmed by clinical interview and/or the Structured Clinical Interview for DSM-V (SCID). A full screening interview will be performed to include medical, psychiatric, and substance use history, and mental status exam. Inclusion and exclusion criteria will again be fully reviewed with the potential subject. The consent documentation will be reviewed with the subject and all participants will provide written informed consent. Subjects will be monetarily compensated for their time spent in the initial screening visit regardless of their subsequent involvement in the study.

Similar to previous studies related to impulsive aggression in schizophrenia,[36] at baseline subjects will be administered the Brief Psychiatric Rating Scale (BPRS), the Barratt Impulsiveness Scale to measure trait impulsivity,[65] the short version of the UPPS-P (S-UPPS-P) to measure urgency and related impulsive constructs,[66] the Buss-Perry Aggression Questionnaire[67] to determine aggressive attitudes, and the Kaufman Brief Intelligence Test-2 (K-BIT-II). Subjects will provide urine samples to test for cotinine to confirm smoking abstinence, and they will also provide urine samples for urine pregnancy testing (if female) and toxicology. Electrocardiograms will be obtained as part of the screening medical evaluation. At the conclusion of the screening visit, if the

subject qualifies for the study and gives informed consent, the subject will be scheduled to return for day 1 of the study.

In some instances, the screening visit will be combined with the first testing session. This is to reduce the logistical burden for subjects for whom transportation may be difficult, as well as for individuals who may have difficulty getting time off from work. It is anticipated that this will reduce the number of subjects who drop out from the study without compromising subject safety.

6.2 Testing: days 1 and 2

Testing occurs on two days separated by approximately one week, but no sooner than 5 days apart (Figure 1) to facilitate drug washout.[68] Subjects will report to the Vanderbilt Psychiatric Hospital. Female subjects will be administered a point of care urine pregnancy test to confirm absence of pregnancy. Subjects will have affixed to their skin a 7 mg nicotine patch or identical appearing placebo, covered by surgical tape so that neither the subject nor the investigator can determine the identity. Previous studies of serum nicotine concentration suggests two hours post-patch application represents an approximate time of peak serum concentration in most subjects[69] and is consistent with previously published protocols.[60, 61] Subjects will begin the behavioral task accompanied by EEG monitoring *at the latest* 120 minutes after patch placement, and will complete the task approximately 12 minutes later. At they time they will provide a saliva sample. This sample will be affixed solely with a non-identifiable code, frozen, and shipped to Dr. William Kem, University of Florida, for analysis of salivary nicotine which has been shown to correlate with serum nicotine levels[70] and eliminates the need for venipuncture. The patch will then be removed.

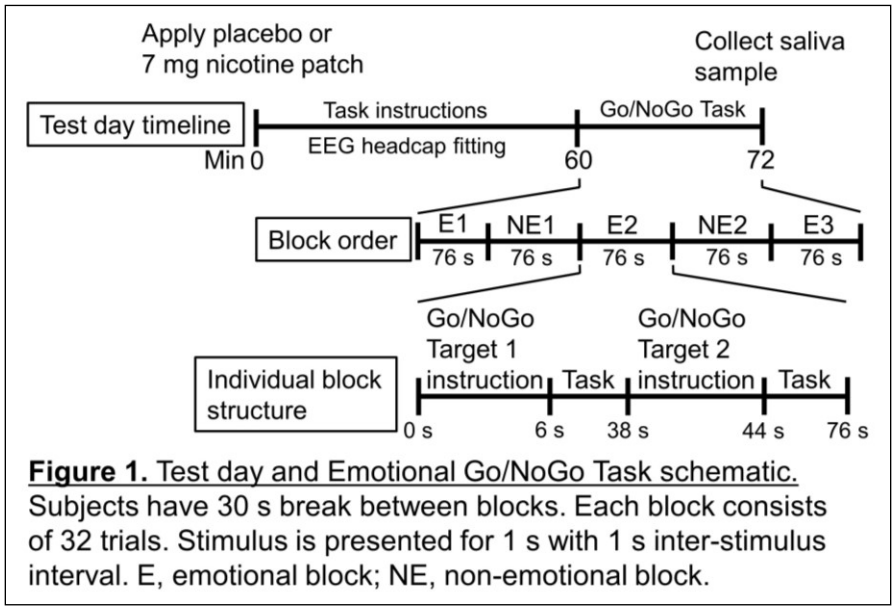

Figure 1. Test day and Emotional Go/NoGo Task schematic. Subjects have 30 s break between blocks. Each block consists of 32 trials. Stimulus is presented for 1 s with 1 s inter-stimulus interval. E, emotional block; NE, non-emotional block.

As noted above, up to two hours after nicotine or placebo patch placement, subjects will begin participation in an Emotional Go/NoGo task, based on the procedure described by Egashira et al,[40] which compared medicated subjects with schizophrenia to healthy subjects and found the patient group was significantly more affected by negative emotional valence than were healthy controls despite only modest group differences with neutral valence stimuli. Subjects will also undergo electroencephalography during performance of the behavioral task. Fearful, sad, angry, and disgust faces (negative valence) and neutral faces will be taken from UPenn's publicly available PERT-96 color emotional stimuli bank.[71] The entire task takes ~12 mins, including breaks, and is

performed in 5 blocks of 32 trials, with 3 emotional blocks with angry/fearful/sad/disgust faces and 2 non-emotional blocks (Figure 1). Each stimulus is presented for 1 s with a 1 s interstimulus interval. In each block the subject is instructed on the go/no-go targets, each comprising 50% of the task stimuli, with instructions changing at the halfway point in each block. Each block contains two instructions. For example: Emotional blocks: go-angry/nogo-fear or go-fear/nogo-angry; Non-emotional blocks: go-male/nogo-female or go-female/nogo-male (Figure 2). Error rates and reaction times are recorded.

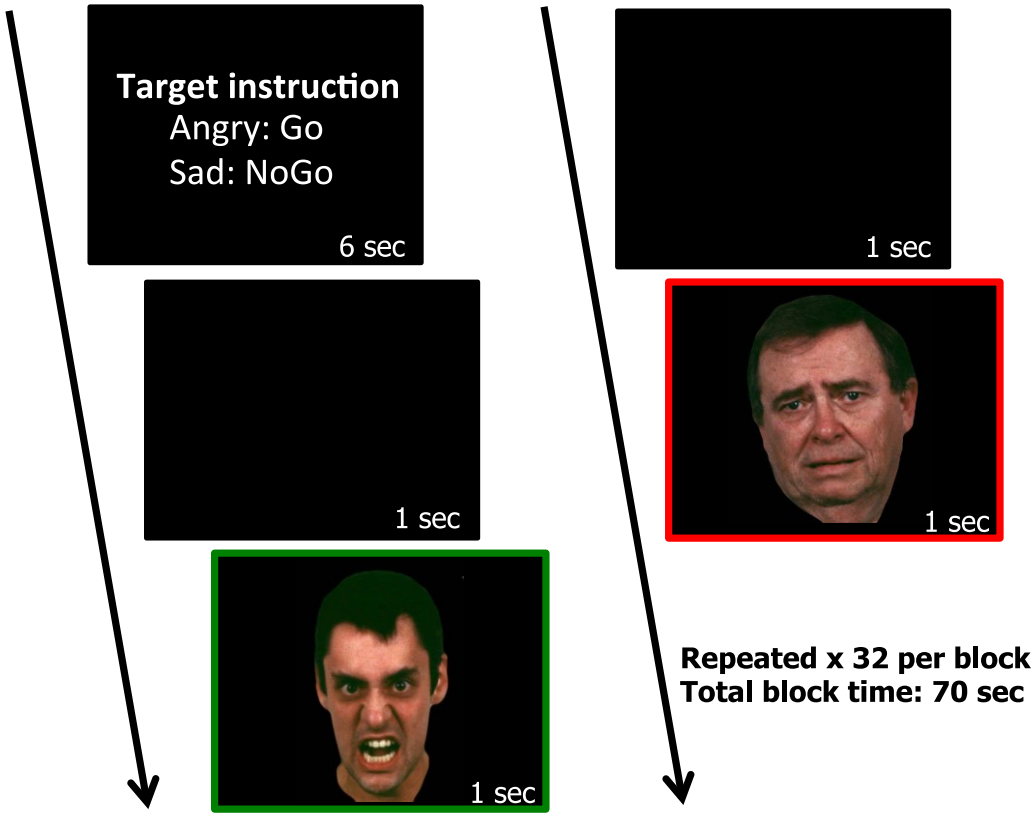

Figure 2 Emotional Go/NoGo schematic. Subjects are given a target instruction at the start of each block for 6 seconds. There is 1 second of blank screen between each 1 second stimulus presentation. In this schematic, the subject would press a key ("Go") when presented with the first stimulus (angry; green border represents the correct response is "Go". This border would not be present in the actual task), and withhold pressing a key for the second stimulus (sad; red border).

Subjects will be monitored for at least 30 minutes after patch removal to confirm the absence of side effects that would compromise their safety upon leaving the hospital.

Subjects will return for day 2 of testing not less than 5 days following day 1. On day 2, subjects will receive the treatment they did not receive on day 1. They will be asked a series of standard questions to assess for the presence of any side effects following their initial study day. If female, they will again be administered a urine pregnancy test to confirm the absence of pregnancy. The remainder of the procedure will be identical to day 1.

7 Study drug

7.1 Background

Please see section 3.2 for a description of acute transdermal nicotine use in humans for cognitive and behavioral outcomes.

7.2 Drug source

Nicotine patches will be purchased from a commercial source and provided to subjects free of charge. The investigators will provide the study drug through project funding by the National Institutes of Health and Vanderbilt University Medical Center Department of Psychiatry and Behavioral Sciences.

7.3 Storage, preparation and use

Nicotine patches will be stored according to manufacturer's instruction. Prior to use, all patches will be covered with surgical tape. Patches will be prepared by an unblinded staff member of the Vanderbilt Center for Cognitive Medicine (CCM) who is not affiliated with the study but is responsible for drug randomization. For subjects who are to receive active drug on that day, the backing will be peeled off the patch and affixed to the subject's arm and sealed in place by surgical tape. For subjects who are to receive placebo on that day, the backing will be *not* be peeled off the patch, and the patch will be affixed to the subject's arm and sealed in place by surgical tape. The CCM staff member will affix the patch in all cases, in general to the upper arm so that the patch will subsequently be hidden below sleeves.

7.4 Justification for the use of placebo

The study is a crossover trial whereby all participants will receive one dose of nicotine and all participants will receive one dose of placebo. As this study is not designed to treat symptoms for a clinical benefit, we anticipate no potential harm that may come to the participant as a result of receiving placebo. Subjects will continue on their outpatient medications during this study.

8 Risks, minimizing risks, and potential benefits

8.1 Risks

The reasonably foreseeable risks to subjects in this study include a) study medication, b) psychological and behavioral assessments, and c) breach of data security and privacy. There may also be unknown or unanticipated adverse effects.

8.1.1 Study medication: transdermal nicotine

Side effects of transdermal nicotine exposure have been well characterized, and participants may experience nausea, headache, skin irritation, palpitations, and dizziness. These side effects were found to be dose related in healthy, non-smoking subjects, with 15 mg nicotine patch significantly less likely to cause side effects than higher dose such as 30 mg.[72] Specifically, in this study 8 non-smoking patients were given a 15 mg nicotine patch. Five of 8 patients experienced mild nausea and lightheadedness after one hour, while 3 of 8 did not have any side effects. Seven of 8 patients continued with the study. Other studies have demonstrated that development of nicotine side effects is highly related to rate of increase and peak concentration of plasma nicotine.[69] Studies of chronic transdermal nicotine in non-smoking populations are very encouraging regarding tolerability. In a large study of transdermal nicotine for treating mild cognitive impairment in older adults, tolerability was excellent in the over 30

subjects randomized to nicotine treatment.[73] Transdermal nicotine use has been successfully reported in case series or trials of patients with advanced dementia and age, a population that is likely to be increasingly sensitive to nicotine than younger, healthier subjects in this study.[29, 30, 73-75]

The question of development of physiological dependence or even nicotine use disorder secondary to patch exposure in non-smoking participants is an important one. The likelihood can be based on previous studies in non-smoking participants that were conducted for significantly longer periods of time than in the proposed study. Nicotine patch has been used for 4-weeks in patients with mild-moderate Alzheimer's Disease for 16 hours per day, initially using 5 mg patches for 7 days, 10 mg patches for 14 days, and finally 5 mg patches for 7 days.[74] In general, patches were well tolerated, with only one of 8 subjects discontinuing. There were no observed nicotine withdrawal symptoms in these participants. Sleep interruption was not problematic as the patches were removed at bedtime. An almost identical study was performed with 15 subjects with age-associated memory impairment using the same nicotine patch dose.[75] Only one of 15 subjects withdrew from this study due to nicotine-related side effects, in this case, nausea. In this study, the most common side effects were local skin irritation, mild nausea and abdominal discomfort, and lightheadedness. Two subjects reported palpitations, but there was no change in body weight, blood pressure, or heart rate in subjects receiving nicotine compared to receiving placebo. No subjects appeared physiologically or psychologically dependent on the nicotine patches. In a 6-month trial of transdermal nicotine or placebo to treat mild cognitive impairment, no subjects (0 of 34 subjects) developed withdrawal or continued to use nicotine products following the study.[73] Data from studies of smokers, who might be predisposed to difficulty discontinuing nicotine-containing products, demonstrated that difficulty with discontinuation of transdermal nicotine after use for smoking cessation was rare (2%), with the percentage of smokers continuing to use nicotine replacement products proportional to the rate of nicotine delivery.[76] Taken together, these previous studies are reassuring regarding the safety of nicotine products from an addiction potential standpoint in non-smoking subjects.

8.1.2 Psychological assessments and Emotional Go/NoGo task

At screening, subjects will undergo non-invasive psychological assessment of a structured nature that has been consistently used without adverse effects in previous studies with a similar subject population. On testing days, subjects will perform the Emotional Go/NoGo task to measure impulsivity in an emotional context, a behavioral construct related to impulsive aggression. This task has been administered to healthy controls as well as patients with schizophrenia without report of adverse events.[36] There is the potential risk that subjects may become fatigued during the performance of screening assessments or behavioral tasks, and that discussion of personal issues with study personnel in the context of screening issues may be stressful or uncomfortable. Because subjects participating in this study will be stable outpatients, it is unlikely that the stress posed by such measures will exacerbate baseline psychiatric symptoms.

8.1.3 Electroencephalography (EEG)

Subjects will undergo (EEG) using an EEG cap while performing the emotional Go/NoGo task. The risks of EEG are minimal and include risk of mild discomfort while wearing the EEG cap.

8.2 Minimizing Risks

8.2.1 Risk of study medication

Dependance: Please see above for a discussion regarding the risk of development of dependence. We chose transdermal delivery of nicotine because its slow rate of delivery significantly reduces the risk of dependence development.[76]

Discomfort: The potential for discomfort will be clearly explained to subjects. Subjects experiencing discomfort who wish to have the patch removed will immediately have their patch removed, and symptoms will subside shortly thereafter. Placebo patches will be handled in exactly the same manner, with the same ability to remove as described above. It should be noted that nicotine patches have been used successfully in populations with cardiovascular disease.[77] Although subjects with known cardiac conduction abnormalities or poorly treated hypertension as assessed during screening will be excluded, these data are reassuring given the possibility of enrolling a subject with a previously undiagnosed cardiovascular condition.

8.2.2 Risk of psychological assessments and Emotional Go/NoGo task

The primary protection against risk for this aspect of the study is the continuous explanation of study procedures, the reasoning for their use, ongoing confirmation that subjects understand these explanations, and consistent communication of the voluntary nature of the study. While it is very unlikely, there is always the theoretical risk of exacerbation of psychiatric symptoms in individuals with schizophrenia due to stressful experiences. Again, a thorough understanding of assessments and behavioral tasks mitigates this risk. The use of standardized Subject Monitoring and Emergency Procedures, described below, will further guard against harm to subjects in the event of exacerbation of psychiatric symptoms.

8.2.3 Electroencephalography (EEG)

The risks of EEG are minimal. Potential discomfort of wearing the EEG cap will be minimized by ensuring the correct fitting on the subject's head.

8.2.4 Risk of breach of data security and privacy

Data obtained from human subjects will be confidential and accessed only by members of the study team with appropriate IRB and HIPAA training, as assured by standard training protocols at VUMC. Data is maintained and secured in locked file cabinets or on encrypted, password protected computers, located in locked offices, and following Health Insurance Portability and Accountability Act (HIPAA) guidelines and the policies and procedures of VU and VUMC. Individuals will be identified by a numerical code that will be kept separate from study data.

8.2.5 Subject Monitoring and Emergency Procedures

Throughout the baseline assessment and two study days subjects are closely monitored by an experienced clinical research team, under the supervision of Dr. Lewis. Subjects performing the Emotional Go/NoGo task and electroencephalographic recording will be monitored by at least one member of the research team. All members of the research team are familiar with the established VU/VUMC emergency plans in the case of a medical or psychiatric emergency. In the case of a medical emergency, a medical response team at VPH will provide immediate first aid and if deemed necessary, emergency medical services will be called by the VPH staff. VUMC's Emergency Department is located one block away from VPH enabling rapid medical care. In the case of a psychiatric emergency, a crisis response team at VPH will respond, which has extensive training in crisis situations. Further crisis evaluation can be performed at VPH or VUMC Emergency Department, and though extraordinarily unlikely, inpatient psychiatric care can be provided through VPH. Dr. Lewis is a credentialed attending physician at VPH and can help arrange for this level of treatment should the need arise.

8.3 Potential benefits

Subjects participating in these studies will receive basic medical and EKG assessments at no cost to them. Otherwise, there are no direct benefits to the subjects participating in this research. The long-term potential benefit of this study is a mechanistically directed approach toward treatment of impulsive aggression arising in serious psychiatric disorders. Every research study requires the potential benefits to outweigh the potential risks of the study. The potential benefit of reducing the burden of impulsive aggression is significant for public health, including for patients, their families, communities, healthcare systems, and criminal justice systems. While the study procedure confers greater than minimal risk, the low likelihood of serious adverse effects is outweighed by the potential public health benefits stemming from the potential results of this study and subsequent studies based on these results.

9 Research alternatives and economic considerations

9.1 Alternatives to participation in the study

This is not a treatment study. Therefore, the study subjects may continue their usual outpatient treatment. If the subject is interested in identifying outpatient treatment options for their psychiatric disorder, the study staff may help the subject identify appropriate locations.

9.2 Payments for participation

All study subjects will be remunerated $25 for completion of the screening visit, regardless of their decision to enroll in the study or their eligibility to enroll. Because of the crossover nature of the study, subjects only yield meaningful primary outcome data if they complete both testing session. They will therefore be compensated an additional $100 at the completion of their *second* testing visit. They will *not* be compensated if they only complete one testing visit. This incentivization is designed to yield greater benefit from the research, thereby improving the risk/benefit ratio of the study. Subjects driving a private vehicle will also be reimbursed for travel expenses at the current IRS business mileage rate and reimbursed for four hours of parking or reimbursed for the cost of an entire day of bus fare. Taxi fare or related (i.e. Uber, Lyft) will not be reimbursed. Subjects must provide appropriate receipts to the study staff.

9.3 Costs for participation

As noted above, subjects will be reimbursed for travel to the study site. All procedures will be provided to subjects at no cost. This includes an electrocardiogram, as described above in detail. Study drug will be provided at no cost.

9.4 Medical treatment in case of injury

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, the subject will be provided immediate medical care at Vanderbilt to treat the injury at no cost to the subject or the subject's insurance. In the absence of an immediate need for medical care, there will be no additional medical treatment available to subjects above and beyond what was available prior to initiating the study. Either licensed physicians or study staff working directly with licensed physicians will conduct the study visits. Emergency medical treatment is available at VUMC, less than one block from VPH. All study subjects will be able to contact study staff throughout their enrollment in the study. Study subjects will be informed regarding the policy noted above. Subjects will obtain treatment either from their current outpatient physicians or via emergency medical services, as recommended by the study physician. There are no limits to the treatment provided. Treatment decisions will be made entirely by the patient's outpatient physician or emergency medical provider and will not be affected by the individual's participation in the study. This is clearly described in the consent form. Study subjects will have the contact information of a licensed study physician at all times who will be available for consultation to determine whether the patient should seek medical treatment during the study.

10 Reporting of adverse events or unanticipated problems involving risk to participants or others

The investigator's assessment of the overall risk level for subjects participating in this study is moderate.

The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with transdermal nicotine administration as minimal risks.
2. Given the established safety of transdermal nicotine in prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

10.1 Greater than minimal risk Data and Safety Monitoring Plan

10.1.1 Personnel responsible for the safety review and its frequency

The principal investigator, Alan Lewis, M.D., Ph.D., will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). He will perform this duty in close consultation with his academic mentors, Paul Newhouse, M.D. and Stephan Heckers, M.D. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator (Dr. Lewis), mentors (Drs. Newhouse and Heckers), or the IRB have the authority to stop or suspend the study or require modifications. A review of the study will be submitted annually to the Vanderbilt Human Research Protections Program (HRPP)/IRB as well as to the NIMH included in the annual progress report

10.1.2 Attribution of adverse events

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Alan Lewis, M.D., Ph.D.) according to the following categories:

1. Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
2. Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
3. Possible: Adverse event may be related to investigational procedures(s)/agent(s).
4. Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
5. Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

10.1.3 Plan for grading adverse events

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

10.1.4 Plan for determining seriousness of adverse events

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;

4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

10.1.5 Plan for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs, including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. *Adverse* events will be reported to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the VU IRB/HRPP via telephone. All related events involving risk but not meeting *prompt* reporting requirements will be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.**

10.1.6 Plan for reporting adverse events to co-investigators on the study, DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

The following individuals, funding, and/or regulatory agencies will be notified:

- All Co-Investigators listed on the protocol.

- National Institutes of Health/National Institute of Mental Health. Notification will be to the attention of the Program Official assigned to the award supporting this study, Mark Chavez, Ph.D., mark.chavez@nih.gov, (301) 443-8942.

The principal investigator (Alan Lewis, M.D., Ph.D.) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

11 Study withdrawal/discontinuation

Subjects may request to withdraw from the study at any time for any reason by contacting the study principal investigator or research team. Requests may be made via email, phone, or in writing, and study coordinator contact information will be provided on the study consent document. If the subject does not provide a reason for discontinuation, the study team will ask the subject if he/she would like to provide a reason for discontinuation, in the hopes to improve subject retention in the future.

Every reasonable effort will be made to maximize subject retention. However, reasons for removal of participants from the study include the following:

- Adverse experience: The participant has experienced an adverse event that, in the opinion of the investigator, requires early termination.
- Death
- Safety risk: Any participant who becomes a safety risk during the trial will be withdrawn.
- Protocol violation: The participant fails to meet protocol entry criteria or did not adhere to protocol requirements.
- Non-compliance: The participant is non-compliant with completion of study-related evaluations and or use of study drugs.
- In the investigator's judgment, it is in the participant's best interest to discontinue participation in the treatment/study.
- Consent is withdrawn. The participant wishes to withdraw from the study, or the legally authorized representative wish the participant to be withdrawn.
- Lost to follow up. Participant could not be recalled back to conduct treatment visit(s)

12 Statistical considerations

12.1 Power analysis

Power analysis for error rates and reaction times is based on effect sizes from previous studies of the Emotional Go/NoGo task in subjects with schizophrenia[40] and our preliminary data from a secondary analysis of a clinical trial of the alpha-7 nicotinic agonist GTS-21. With a sample size of 25 subjects, we will achieve 80% power at □lpha = 0.05 to detect a difference from 35% to 10% in the omission error between two experimental conditions within a subject (expected correlation of 0.60) and to detect an effect size of 0.6 in the mean reaction times between the control and intervention conditions within a person using paired t-test at alpha = 0.05. The dropout rate in a similar published acute crossover study of schizophrenia patients was ~15%.[78] We thus anticipate needing to enroll 30 subjects to result in 25 completers for an appropriately powered study. We will match this group with a healthy control sample of similar size.

12.2 Data analysis plan

Omission error rate will be analyzed using non-linear mixed effects modeling of a binary outcome omission error (0/1), while reaction time will be analyzed with a linear mixed effects model. In both models, there will be a random effect for subject, a primary fixed independent predictor treatment condition (nicotine or placebo), an independent adjustment variable block valence (emotional vs. non-emotional task), and the interaction of the latter two predictors to examine whether the omission error rate or reaction time between two treatment conditions is moderated by the valence. Significance will be established at alpha = 0.05.

We expect nicotine will reduce error rates in control blocks consistent with previous reports of improved attention with acute dosing of transdermal nicotine.[51, 52] We expect to find an interaction between valence and treatment such that performance improves with nicotine to a significantly greater extent in negative valence blocks. We further expect this increase to be more prominent in individuals with schizophrenia than in healthy controls. We expect salivary nicotine concentration, which is proportional to serum nicotine,[70] will correlate with improvement in response inhibition. Based on previous findings in the Emotional Go/NoGo task,[40] we do not expect to find an effect of antipsychotic exposure, as measured by chlorpromazine equivalents.

12.3 Inclusion of men and women

We do not expect significant difficulties in patient recruitment based on previous studies with similar patient populations conducted in the Heckers Lab. Men and women will be included in this study. Unlike highly sexually dimorphic rodent aggression, multiple studies find no significant gender difference in physical aggression amongst inpatients with schizophrenia.[79, 80] Given these previous findings and the above power analysis, it is outside the scope or resources of this focused study to power sufficiently to include sex/gender as a formal variable in our experimental design. However, all efforts will be made to recruit similar numbers of men and women to the study, final reported data will be disaggregated by sex/gender, and *hypothesis-generating* comparative analyses will be performed that can be pursued in future, *hypothesis-testing* prospective studies. Previous studies of nicotine for cognition in schizophrenia enrolled men and women, but no differences in their response to drug were reported.[60, 61] The inclusion of drug plasma levels can mitigate pharmacokinetic-based differential responses between men and women, and will be done in the proposed study.

13 Privacy/confidentiality issues

Data obtained from human subjects will be confidential and accessed only by members of the study team with appropriate IRB/HIC and HIPAA training, as assured by standard training protocols at Vanderbilt University Medical Center. Data is maintained and secured in locked file cabinets or on encrypted, password protected computers, located in locked offices, and following Health Insurance Portability and Accountability Act (HIPAA) guidelines and the policies and procedures of Vanderbilt University and Vanderbilt University Medical Center. Individuals will be identified by a numerical code that will be kept separate from study data.

14 Follow-up and record retention

The estimated duration of the data collection phase of the study is four years. Identifying information will be deleted (in the case of digital data) or destroyed by shredding using clinical shredding bins by the principal investigator or trained study personnel at the conclusion of the data collection phase of the study. The non-identifying study data will be transferred to a portable hard drive and stored in a locked filling cabinet. Non-identifying data stored in the above manner will be retained indefinitely. Only the PI, study coordinator, and research staff will have access to the information.

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