Abbreviated Title: Decision making in anxiety
NIH IRB #: 000378
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Title: Identifying decision making parameters in healthy volunteers (HV) and anxiety patients (AD).

Maryland Pao, MD: National Institute of Mental Health/OCD
Building 10, Rm 6-5340
Bethesda, MD 20892
Phone: 301-435-5770
E-mail: paom@mail.nih.gov

Investigational Agents *(if applicable)***:**

Drug Name:	n/a
IND Number:	n/a
Sponsor:	n/a
Manufacturer:	n/a

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Identifying decision making parameters in healthy volunteers (HV) and anxiety patients (AD).

Study Description: This study's goal is to identify parameters of interest in decision making in the context of anxiety disorders, using theoretical models in healthy volunteers (HV) and anxiety patients (AD). Participants are asked to complete a decision-making task, namely the Multi-armed Bandit Task. The study will be conducted in the clinic.

Participants (HV and AD) are asked to fill out questionnaires and complete the Multi-armed Bandit Task. An electric shock is used as the aversive stimulus. Monetary reward is used as the reward stimulus. Additionally, physiological signals (Heart rate, skin conductance activity, startle) are collected during the course of the task.

In addition, in a pilot study, participants startle responses for varying shock parameters are recorded and analyzed.

Objectives: The primary objective of this study is to use theoretical models in healthy volunteers (HV) and patients with an anxiety disorder (AD) to better understand how changes in anxiety are associated with changes in decision making. In addition, this study will ascertain whether decision making parameters correlate with certain behavioral measures such as trait and state anxiety using (i) questionnaires, (ii) physiological measures.

Endpoints: The primary endpoint of this study is a significant difference in model derived parameters between experimental manipulations (conditions) and/or population groups. The parameters of interest include: 1) Learning Rate, 2) Exploration parameter, 3) Discount rate, 4) Loss aversion, 5) Inverse Temperature.

The secondary endpoints are a significant correlation between functions of model derived parameters and behavioral and/or physiological measures of anxiety including:

1) Questionnaire scores
2) Startle
3) Skin conductance

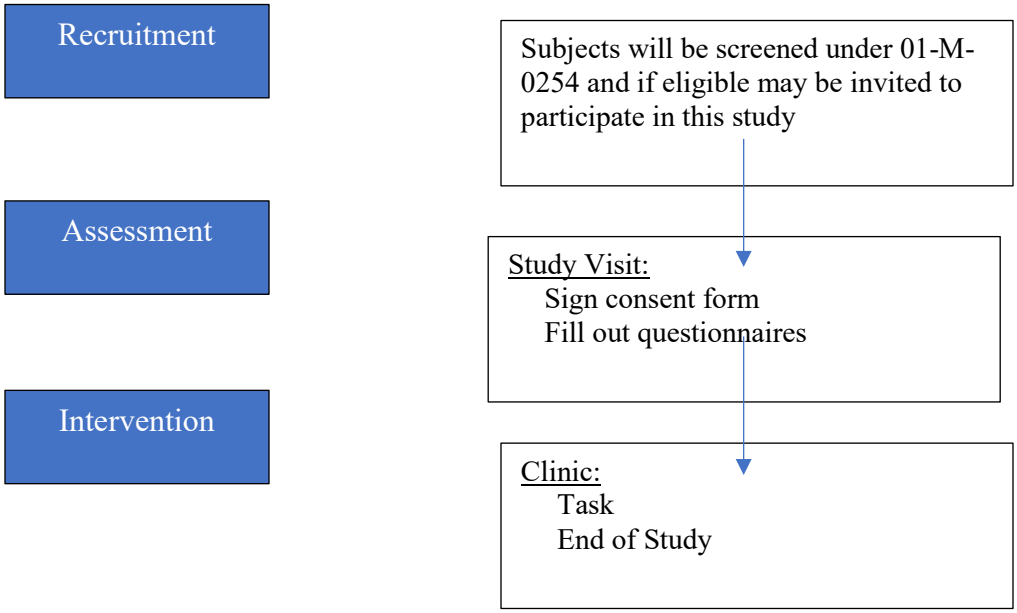
Study Population: Participants will be males and females, 18 years and older. They must be English-speaking. The study population will include patient and volunteer participants. Number of participants:

1)
   Multi-arm Bandit task: 80 (40 HV, 40 AD)
   Pilot: 20 HV

Description of Sites/Facilities Enrolling Participants:	TOTAL ACCRUAL CEILING: 100 volunteers Single-site study at National Institutes of Health
Description of Study Intervention:	Multi-arm Bandit task. Electric shocks: Electric shocks are used as aversive stimuli. Electric shocks are one of the most efficient ways to induce anxiety in the laboratory. The shocks will be delivered through two disk electrodes located on the forearm or on two fingers Auditory startle: The startle reflex will be elicited with a 102 dB white noise (40-ms duration) delivered binaurally via headphones.
Study Duration:	12 months
Participant Duration:	One outpatient visit

1.2 SCHEMA

Figure 1: Schematic of Clinic Study Visit



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Study Visit
Informed consent	X
Concomitant medication review	X
Vital signs	X
Pregnancy test**	X
Adverse event review and evaluations	X
Questionnaires #	X
Multi-arm Bandit Task	X
Electric shocks	X
Auditory startle	X
Complete Case Report Forms (CRFs)	X

*Screening to be conducted under 01-M-0254 screening protocol and consent. Screening may also happen under 17-M-0181.
**Pregnancy test in females only.
***Study visits are single visit outpatient studies
A complete list of the questionnaires used is included in section 3.1.4

INTRODUCTION

1.4 STUDY RATIONALE

Anxiety disorders are characterized by aberrations in the processing of and response to threat, such as (1) Exaggerated threat appraisal, (2) Over generalization, (3) Persistent avoidance. These aberrations result in impaired decision making. In the recent past, a few studies have started to ask questions regarding the influence of anxiety on decision making using theoretical models. However, there is a number of avenues that can be taken to extend these efforts. Firstly, previous studies do not consider specific decision-making parameters due to limitation in their task design. Secondly, the validity of these parameters needs to be confirmed using different study designs and larger sample sizes. Finally, the links between anxiety symptoms and specific parameters need to be examined and established. The present study will ascertain and open new avenues for understanding decision-making perturbations in the anxiety and provide basis for the optimization and development of novel treatment strategies.

1.5 BACKGROUND

Fear and anxiety are normal adaptive responses to threat. Anxiety is considered pathological when it is either excessive or inappropriate to the context. The influence of anxiety goes beyond the subjective feelings and autonomic reactivity. Indeed, anxiety powerfully affects motivated behavior. The majority of experimental tasks, used to probe behavior in anxiogenic environments or in response to aversive cues, usually focus on only one aspect of behavior. For example, previous studies by our group have targeted cognitive constructs like working memory (Balderston et al., 2016; Balderston et al., 2017), response inhibition (Grillon et al., 2017), or attention. Each of these cognitive processes contributes to decision making, the backbone of motivated behavior.

In this study, we propose a holistic approach that evaluates many decision-making facets. Decision theory is a framework that permits to quantitatively understand optimal (maximizes rewards and minimizes punishments) and sub-optimal behavior in various environments ((Dayan & Daw, 2008)). This framework employs ideas from reinforcement learning (Sutton & Barto, 1998), in which agents learn to adapt their behavior in function of rewards and punishments and optimize goal-directed behavior.

One aim of decision theory is to develop mathematical models that approximate human behavior. These models have parameters which are optimized to fit behavior. The values of the fit parameters could help evaluate individual and group differences in decision making strategies that are not tractable otherwise. Recent papers have used decision making models to extract parameters of interest in the context of anxiety. For example, Charpentier et al. (Charpentier, Aylward, Roiser, & Robinson, 2017) considered parameters that contribute to loss aversion and risk aversion in decision making. Browning et al. (Browning, Behrens, Jocham, O'reilly, & Bishop, 2015) probed the rate of learning in volatile vs. stable scenarios. A number of decision-making models could not study parameters separately, which prevent the possibility to isolate the influence of individual parameters, and thus limit their usefulness. The issue lies in the fact that while the parameters themselves are distinct and separable, their estimation is not (Daw, 2011). For example, the estimation of two such parameters 'softmax temperature' and 'learning rate' may be correlated since they have similar effects on the observed data. Experiments that probe the distinct influences of individual parameters of decision making in anxiety could be of vital

importance in furthering our knowledge of the etiology of anxiety and related disorders. Our approach is to study induced anxiety in both healthy volunteers and anxiety patients. We will examine an array of parameters such as learning rate, exploration vs exploitation parameter, inverse temperature and loss aversion/gain seeking.

1.5.1 Exploration vs exploitation: Multi-arm bandit Task

Everyday decision-making requires individuals to choose among a set of actions and decide on the 'best action'. This process involves learning the consequences of a particular action (either rewarding or punishing) and building an internal representation (value) associated with a particular choice. In a reinforcement learning framework, rewards and punishments are used to update the value associated with an action (Dayan & Daw, 2008). The learned value is then used to frame a policy for future actions. The optimal policy would result in the most favorable future outcomes. For example, a policy can be centered on the role of exploration in making decisions. Depending on whether the scenario is volatile on stable, different policies would be optimal. (A stable scenario is one in which the action-outcome relationship has few or no changes). In a stable scenario, the optimal policy would be to explore among the choices only when there is a mismatch in the perceived outcome. Similarly, in a volatile scenario, random sampling among the actions would result in better outcomes in the long run. Previous work has shown that anxious individual have difficulty in learning whether action-outcome associations are volatile or stable (Browning et al., 2015). Such similar differences could also arise in the exploration-exploitation trade-off: Should an individual increase their exploration and get a better understanding of the action-outcome contingencies or should the individual minimize exploration in order to exploit the contingencies already learnt? The optimal policy would thus be elucidated by the exploration parameter.

1.5.2 Pilot studies

Rewards and punishments form the basis for decision making. For the purposes of this study money is used as the reward and electric shocks are used as the punishments. The rewards or punishments received have underlying dimensions. These include the magnitude, duration, frequency and probability of the rewards or punishments. Startle responses, which are an indication of physiological fear and/or anxiety would change depending on the parameters of the electric shock. Previous work has assessed some of these dimensions. For example, one study used predictable and unpredictable timing and varied the intensity of shock (Shankman, Robison-Andrew, Nelson, Altman, & Campbell, 2011). Another study examined the role of cue and temporal unpredictability (Davies & Craske, 2015). The difference between occurrence uncertainty and temporal uncertainty was the focus of yet another study (Bennett, Dickmann, & Larson, 2018). However, a comprehensive study that examines each of these parameters in a single study has not been conducted. [Note: The upper and lower bounds of these parameters will be assessed using the procedure mentioned in Auxiliary methods 4.1.3)]

1.6 RISK/BENEFIT ASSESSMENT

1.6.1 Known Potential Risks

Questionnaires: There is minimal medical risk in completing the questionnaires. Some of the questions may make the participants feel uncomfortable or anxious. Participants may refuse to answer any question or to stop a test at any time and for any reason.
Psychophysiological recording: The psychophysiological measures that will be obtained are non-invasive, requiring the administration of no needles, drugs, or dyes. Little discomfort is expected. During electrode placement, the possibility of skin irritation from contact with the saline electrode paste exists. However, this is unlikely as the salt concentration of the paste is similar to that of human sweat. The risk is equivalent to that of an EEG recording.
Electric shock: The shocks will be delivered through two disk electrodes located on the subject's left wrist. The PI has extensive experience with shocks. The shock is generally described by subjects as anxiogenic and uncomfortable. The mean rating of aversiveness on a scale of 1 (not painful at all) to 10 (extremely painful) is about 5. Over 95% of subjects who experienced the shock chose to participate in the experiment.
In very rare occasions, subjects have experienced symptoms that may be related to the shock. A participant with a condition called "cubital tunnel syndrome," a repetitive motion injury similar to carpal tunnel syndrome, indicated worsening of his syndrome over the months subsequent to his participation. Another participant reported pain in her arms for several hours after testing. The pain was no longer present the next day. It is unclear whether these symptoms were due to the shocks. Nevertheless, subjects with neurological symptoms of the wrist and arms will be excluded from the study.
Auditory startle stimulus: The auditory stimuli that will be used in the startle studies are 40-ms duration 102 dB white noise. Auditory startling sounds of much higher intensities are frequently used in startle studies. Sounds of higher intensities and longer duration are also widely used in aversive conditioning in human subjects, where they serve as unconditioned stimuli. The short duration (40 ms) of these sounds makes them safe (i.e., there is no danger of hearing impairment). In addition, a white noise is safer than a pure tone. The PI has been involved in similar studies and collaborations involving over 1000 of subjects with no adverse reactions. The auditory stimulus may trigger a migraine.

Procedures to Minimize Risks

Electric Shock: Shock will be delivered at a level that is judged by the subject as uncomfortable but tolerable. Study shock levels will be determined before the test begins. The subject may stop the experiment at any time if they find the discomfort to be too great.

Confidentiality: We will actively protect confidentiality of the subjects and the data in each step. Information will be stored using a confidential case number, and no identifiers (name, address, etc.) will be used that could allow direct linking of database information to individual subjects. Data will be kept in password-protected computers. Only study investigators will have access to the data.

1.6.2 Known Potential Benefits

There is no direct benefit to the participants but is likely to yield generalizable knowledge about the underlying brain mechanism of fear and anxiety.

1.6.3 Assessment of Potential Risks and Benefits

This is a minimal risk protocol enrolling adult volunteers. The risks are reasonable in relation to anticipated benefit.

2 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to examine whether there are changes in decision making (such as choice learning, exploration) associated with increased or decreased anxiety, by employing theoretical models in healthy volunteers and anxiety patients.	*The primary endpoint of this study is a significant difference in model derived parameters between experimental manipulations (conditions) and/or population groups.* *The parameters of interest include:* *1) Learning Rate* *2) Exploration parameter* *3) Discount rate* *4) Loss aversion* *5) Inverse Temperature*	*Computational models allow for the testing of different decision-making theories in a quantitative fashion. (Daw et al. 2009) and allow for interpretation of trial by trial observations (O'Doherty et al., 2003; Bayer and Glimcher, 2005).*
Secondary		
In addition, this study will ascertain whether decision making parameters correlate with certain behavioral measures such as trait and state anxiety using (i) questionnaires, (ii) physiological measures.	*The secondary endpoints are a significant correlation between functions of model derived parameters and behavioral and/or physiological measures of anxiety including:* *1) Questionnaire scores* *2) Startle* *3) Skin conductance*	*Models estimate parameters involved in the decision-making process which are otherwise subjective in nature (Platt and Glimcher, 1999; Sugrue et al., 2004). The validation of these computational constructs with other physiological and/or behavioral measures are vital for their interpretation. This might help to uncover what is the implication of specific symptoms in*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		influencing specific parameters of decision making.
Tertiary/Exploratory		
In addition, this protocol will pilot studies that measure the effects of changing stimulus parameters (such as amplitude, duration, frequency, probability) on physiological responses and decision making	*The endpoints of this this pilot study are changes in physiological responses as a function of changing stimulus parameters*	*Understanding the relationship between stimulus parameters and physiological responses such as startle, will allow for better measures of anxiety*

3 STUDY DESIGN

3.1 OVERALL DESIGN

The purpose of the clinic experiments is to identify robust differences in model derived parameters.
The study includes one visit that is expected to last 3-4 hours and is designed to have 2 conditions/ scenarios in order to better delineate the model parameters. An additional telehealth consenting visit may occur prior to the study visit. The tasks and related auxiliary procedures are described in the sub-sections below:

3.1.1 Multi-arm Bandit task

As mentioned in the objective section, the primary purpose of the study is to quantitatively assess decision making strategies in aversive and rewarding scenarios and probe their relevance to fear and anxiety. To this end, participants perform a choice making task, where they strive to maximize rewards (if present) and minimize punishments (if present). On each trial, participants are presented with a set of different choices or scenarios. The participant then takes an action OR a set of actions. After a variable time period the participant receives a reward/punishment probabilistically associated with that action. Thus, by repeated sampling among the options, the participant should employ a policy that maximizes reward (monetary) AND/OR minimizes punishment (shocks). After a set of these trials the probabilities associated with the options are changed, such that the participant needs to resample among the options to once again determine the optimal action.
In addition to performing the optimal action, participants may be asked to indicate the probability of reward/ punishment they feel is associated with their action. This way, the participants reveal their expectation of reward AND/OR punishment for the taken action. After a short time interval, the actual probability of reward AND/OR punishment is revealed to the participant.

The two conditions are designed to affect the nature of the optimal strategy, such that in one condition, the highest cumulative outcome depends on purely value-driven exploration; whereas, in the other condition, the best strategy involves adequate random exploration.

3.1.2 Pilot studies

The pilot studies are used to vary the parameters of the shock stimulus in the clinic study, so as to determine the efficacy of the aversive stimuli. Startle responses (see Auxiliary study procedures) which are an indication of physiological fear and/or anxiety are expected to change depending on the parameters of the electric shock. The shock parameters of interest are the amplitude (3 levels), probability (4 levels), resulting in a total of 12 levels. [Note: The upper and lower bounds of these parameters will be assessed using the procedure mentioned in Auxiliary methods 4.1.3)]

3.1.3 Auxiliary study procedures

A subset of the procedures described below will be employed to deliver aversive stimuli and record physiological metrics.

Questionnaires:

Participants will be asked to complete a subset of the following questionnaires:

- State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983): 40-item scale assessing state anxiety (20 items) and trait anxiety (20 items).
- Anxiety Sensitivity Index (ASI;Reiss et al., 1986): 16-item scale assessing anxiety sensitivity in terms of the dispositional tendency to fear the somatic and cognitive symptoms of anxiety due to a belief that these symptoms may be dangerous or harmful.
- Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): 16 items assessing chronic, excessive, and uncontrollable worry.
- Intolerance of Uncertainty Scale short form (IUS-12; Carleton, Norton, & Asmundson, 2007): 12-item scale assessing reactions to impending uncertainty, ambiguous situations, and the future. It consists of two factors: prospective anxiety (7 items) and inhibitory anxiety (5 items).
- BIS/BAS scale (Carver et al., 1992):24 items assessing individual differences in the sensitivity of two motivational systems, the behavioral approach system (BAS) and a behavioral avoidance (or inhibition) system (BIS).
- DOSPERT Risk-taking behaviors scale (RTBS; Weber, Blais, & Betz, 2002): 14-item scale assessing people's willingness to engage in risky decision-making across different risk-taking domains including health/safety, recreation, ethics, social interaction, gambling.
- Positive Affect/Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988): 20-item scale assessing positive (10 items) and negative (10 items) affects.
- Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995): 11-item scale assessing personality/behavioral construct of impulsiveness.
- Sensation Seeking Scale (SSS) Form V (Zuckerman et al., 1978): 40-item scale assessing sensation seeking behaviors according to four dimensions associated with sensation seeking that are thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility.

Curiosity and Exploration Inventory (CEI-II) (Kashdan, T.B., et al.;2009): 10-item scale assessing individual differences in the recognition, pursuit, and integration of novel and challenging experiences and information.

Startle response
The startle reflex will be elicited with a 102 dB white noise (40-ms duration) delivered binaurally via headphones. The eyeblink component of the startle reflex will be recorded binaurally with two electrodes placed under each eye. Eyeblink responses will be scored in the 20-100 ms window following the onset of the startle stimulus.

Autonomic measures
Heart rate, skin conductance activity (event-related responses and spontaneous fluctuations) to evaluate changes in autonomic arousal. The heart rate will be monitored with two disposable electrodes, one on each wrist. A computer algorithm will detect the R-wave in each cardiac cycle and calculate the number of whole and fractional heart beats for 500 ms periods in each condition. The skin conductance will be measured using two Ag-AgCl electrodes filled with a .05M NaCl electrolyte. Electrodes will be placed on the distal phalanges of the index and second fingers of the left hand.

Electric shock: forearm or fingers
Electric shocks are one of the most efficient ways to induce anxiety in the laboratory. The shocks will be delivered through two disk electrodes located on the forearm or on two fingers.
Test shocks
At the beginning of the study a shock workup procedure is conducted to determine the setting for the overall procedure for each subject. The level of shock is initially set at 3.5 μAmp (the low range). A shock is administered and the subject is asked to rate it on a scale from 1 (not at all unpleasant) to 10 (extremely unpleasant but not painful). We then increase the level of shock slightly until the subject identifies the sensation at a rating level of 10. The level is selected based on the subjective ratings provided by the participant. Once the level 10 is ascertained, participants will receive shocks corresponding to that magnitude or lower for the remainder of the study visit. In addition, subjects are reminded that they have the opportunity to withdraw from the study at any time if they wish.
Participant rating of the experience:
At the end of the study subjects are asked to retrospectively rate their experience of the shock on a scale from 1 (not at all unpleasant) to 10 (extremely unpleasant but not painful). This provides us with an assessment of the overall unpleasantness of the experience during the entire shock experiment.

3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rationale for the study design stems from the primary and secondary objectives, namely, to estimate and probe the role of various decision-making parameters in anxiety. To that end, a multi-arm bandit task is utilized which involves specific parameters of interest. The task is to be performed by healthy volunteers and anxiety patients in order to test whether these parameters differ across groups. The clinic study allows the use of electric shocks (which serve as an aversive stimulus and negative reinforcer). Additionally, startle and other physiological signals can be probed in the clinic version of the task.

3.3 JUSTIFICATION FOR DOSE

N/A

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Male or female, aged 18-50, inclusive
3. Patients only: Primary DSM5 diagnoses of an anxiety disorder (GAD, SAD, panic disorder)

4.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Non-English speaking individual
2. Pregnancy or positive pregnancy test
3. Any significant medical or neurological problems as determined by investigators (e.g. cardiovascular illness, respiratory illness, neurological illness, seizure, etc.)
4. Current or past serious mental disorders (e.g., bipolar or psychotic disorders) (except for anxiety and depressive disorders in patients)
5. Current alcohol or substance use disorder
6. History of moderate or severe alcohol or substance use disorder within one year prior to screening
7. Current or past significant organic central nervous system disorders as determined by investigators, including but not limited to seizure disorder or neurological symptoms of the wrist and arm (e.g., carpal tunnel syndrome) for shocks to be delivered on affected arm.
8. Positive urine toxicology screen at screening visit under 01-M-0254
9. Employees of NIMH or an immediate family member of a NIMH employee.
10. Healthy volunteers only: Current DSM-5 disorders.

4.3 INCLUSION OF VULNERABLE PARTICIPANTS

4.3.1 Participation of NIH Staff or family members of study team members

NIH staff and family members of study team members may be enrolled in this study as this population meets the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.
Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.
The NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research will be made available. Please see section **9.1.3** for consent of NIH Staff.

4.3.2 Justification for exclusion of non-English speaking subjects:
We exclude non-English speakers since not all the instruments and test we use are validated in other languages.

4.3.3. Justification for exclusion of subjects over 50 years of age:
As people get older, their startle response decreases[64]. The upper age limit will be 50 years old to minimize the confounding effects of age.

4.3.4. Justification for exclusion of pregnant women:
We will exclude pregnant as the effects of shock are unknown on a developing fetus.

4.3.5. Justification for exclusion of children:
In order to elicit anxiety responses similar to those occurring in anxiety disorders it is important that out stressor is highly unpleasant. We thus chose to use electric shock as the stressor. Though shock stressors are well tolerated by adults (and used frequently in the literature to assess stress reactions in healthy and disordered individuals), such methods may be inappropriate for children. We will not enter children under age 18 because of ethical concerns about exposing them to threat of shock. Moreover, concerns regarding the legal inability to provide informed consent before age 18 (and the consequent dependence on parental decision) preclude inclusion of subjects under age 18.

4.3.6. Justification for exclusion of decisionally impaired adults:
All subjects must be able to provide their own consent. We do not want to enroll participants who do not understand the risk/benefit ratio of the study, particularly when there is no benefit to the participants.

4.4 Inclusion of Pregnant Women, fetuses or neonates

N/A

4.5 Lifestyle Considerations

N/A

4.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).
Individuals who do not meet the criteria for participation in this trial (screen failure) because of personal reason, use of exclusionary PRN medication, or due to a transient medical condition may be rescreened.

4.7 Strategies for Recruitment and Retention

Recruiting
Recruitment will be done by NIMH IRP, Clinical Center Office of Patient Recruitment, and Branch staff. All advertising methods will comply with the most current regulations (NIH and

OHSRP SOPs and guidelines, as well as FDA guidelines for FDA-regulated research) and the NIMH policy on recruitment materials.

Participants will be recruited under the screening protocol 01-M-0254: "The Evaluation of Patients with Mood and Anxiety Disorders and Healthy Volunteers." All recruitment materials (paper or web ads, flyers and listserv announcements) will be IRB approved under this protocol prior to use. Under this protocol recruitment will be done via print media and through advertising on the internet and websites. NIH employees/staff will not be directly recruited by or through their supervisors to participate in this study. NIMH employees/staff and their immediate family members cannot participate in this protocol. We will use the following recruitment methods:

A. *Advertisements*
    i. Print advertisements
    ii. Flyer advertisements
    iii. Online advertisements
        i. Web ads will direct readers to the study specific link on the NIMH Join a Study website.
    iv. Text advertisements
    v. Notecard advertisements
    vi. Postcard advertisements
    vii. Animated storyboard video
B. *Advertising venues*
    i. Internal NIH media (e.g. flyering boards, newsletters)
    ii. NIH Internet (e.g. http://nimh.nih.gov/JoinAStudy)
    iii. Listservs
        - IRB approved ads will be posted on listservs with the permission of the moderator and IRB required statement on how the receiver was identified. Listservs may include provided by OPR or local groups. We will not post/send directly to the listserv. Rather, an email with information about our study information will be sent to the administrator of the listserv, which will include the following disclaimer:
        "You are receiving this message because your email address is included in the above listserv. The purpose of this message is to inform you of our NIMH research studies. The moderator of the listserv has permitted its use for this distribution."
    iv. Print publications (e.g. local or university newspapers, magazines, health care organizations, etc)
    v. Online paid advertising (e.g. university online newspapers, local websites, Facebook, Instagram, Twitter) or unpaid (e.g. NIH Twitter and Facebook accounts such as the NIH record)
    vi. Craigslist (posted under the "Volunteer" category)
    vii. Notecards and/or flyers may be posted on bulletin boards at local establishments including grocery stores, coffee shops, community centers, college campuses, and NIH Clinical Center with approval of the venue or in accord with their policy. They may be made available at outreach exhibits, speaking engagements, and professional meetings with approval of the venue or in accordance with their

policy. Clinicians who are contacted will be provided with information to disseminate to patients as they see fit. We will explain to them that individuals interested in participating in our studies will need to initiate contact with our group and that we will not make this initial contact. Notecards and/or flyers may be given directly to those requesting study information.

viii. Office of Patient Recruitment list of volunteers.

ix. Research Match database

x. Participants screened through NIMH protocol #17-M-0181 titled "Recruitment and Characterization of Research Volunteers for NIMH Intramural Studies" and referred to our study. Data and study procedures done under #17-M-0181 may be used toward eligibility determination.

C. Prescreening Database

i. We may also use the Survey tool in REDCap (Research Electronic Data Capture) to assist with recruitment, pre-screen potential participants, and evaluate our recruitment strategies. REDCap is a secure web application for building and managing online surveys and databases. REDCap Survey will not contain PHI and contains workflows that support the collection of de-identified data. Interested persons may be directed to REDCap from a link in our IRB approved advertisements. In our secure confirmation email to potential healthy participants, we may include the link to offer to allow participants to pass along as a WOM recruitment strategy with the disclaimer that they should not forward the confirmation email. Potential participants will be given an automated survey when they click on the link. The survey would ask the potential participant our non-PII prescreening questions that we currently ask via a phone prescreen. The subject will be provided with a numeric code automatically by the database and will also be provided the phone number for our study staff and will be asked to call our research team to continue screening. The potential participant will be instructed to provide their unique numeric code during this phone screen. The unique code will allow the staff to connect the person to the non-PII information that has already been entered by the potential subject. This allows us to speed up the prescreening process as we will have access to their answers. We will be the only ones with access to the responses. We will also use REDCap to develop an anonymous survey to evaluate our screening efforts.

4.7.1 Costs

There is no cost to participate.

4.7.2 Compensation

Volunteers will be compensated for time and research-related inconveniences. Participants in the clinic study will be given $120 for their participation in the single outpatient visitThese tasks use monetary incentives to assess motivation. Participants may win up to an additional $25 in the study task. Subjects may also be compensated an additional $20 if they complete an extra visit for Telehealth consent.

Travel is not compensated. If subjects do not complete the study they will be paid half of the compensation. NIH employees or staff who participate during work hours must have permission from their supervisor. NIH employees or staff must either participate outside of work hours or take leave in order to receive compensation. We will use the NIH payment system to provide

compensation. Participants with direct deposits set up will receive it via direct deposit within 6 to 8 weeks.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTIONS(S) ADMINISTRATION

5.1.1 Study Intervention Description

There will be no IND obtained for the use of any of the commercial agents used in this study.

The devices used in the study are not used to diagnose, treat, prevent, cure, or mitigate any disease or condition. The devices are not being studied in this protocol and are not part of the research question. The devices are used as study procedures in the task to provide a threat (shock or startle device) without the purpose of diagnosis. There is no known increase of risk using these devices.

The devices used on the study include the following:

IDE	Manufacturer/mnodel	Device Size	Description of Components	Settings/applications	Approved for indications
Shock device	Digitimer DS7A	225 x 100 x 255mm (w x h x d)	Input: electrical via BNC socket on rear panel Output:rear panel BNC, positive TTL pulse 1 ms wide	Settings: initially set at 3.5 mA and individually determined by subjects during shock workup based on subject rating of aversiveness. Maximum possible current setting of the device is 99.9.mA. Duration: 100 ms Frequency: NA. Single pulse of 100 ms given 12 times per session	Yes*
Startle device	N/A	100mm x 60mm x 25mm	Teensyboard 3.2, Audio adaptor board for Teensy 3.0 – 3.6	Settings: 103 dB output Duration: 40ms Frequency:	Yes*

*Shock device, and startle deviceare FDA approved devices and are not attempting to serve as a new indication nor an increased risk from their indication. It is not being used for treatment in this study but used in a research setting as aversive stimulus (shock and startle) in healthy and anxiety volunteers. The shock device and auditory startle have been used in our 01-M-0185, 02-M-0321, and 03-M-0093 protocols for almost two decades without significant adverse events. This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a change in the route of

administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. The route of administration and dosage used in this study is identical to those used in patient populations. The study intervention is commercially available but is not being used in accordance with approved labeling, specifically the population/disease as this protocol uses it on healthy volunteers.

Acoustic startle and shock device used in this protocol are considered non-significant risk (NSR) devices and will only be used within published guidelines.
Auditory startle and shock device do not meet criteria for a Significant Risk device as outlined Under 21 CFR 812.3(m), as an investigational device that:
1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
Response: Auditory startle and shock device are not implantable devices.
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
Response: Auditory startle and the shock device are not for use in supporting or sustaining human life. They do not present a potential for serious risk to the health, safety, or welfare of participants when used as described in this protocol.
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject
Response: Auditory startle and shock device, as used under this protocol is not of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety or welfare of a subject.
4. Otherwise presents a potential for serious risk to the health, safety or welfare of a subject
Response: Auditory startle and shock device have been in use numerous for decades and have been cleared by the FDA. Safety guidelines have been developed and updated allowing its dissemination to a wide range of clinical and non-clinical settings. The FDA has generally waived pre-IDE inquiries for auditory startle and shock device studies on a NSR device basis. Hence, the NIH IRB, like most US IRBs, has accepted NSR designation for auditory startle and shock device within these limitations.

5.1.2 Dosing and Administration

Not applicable.

5.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Not applicable.

5.2.1 Acquisition and Accountability

Not applicable.

5.2.2 Formulation, Appearance, Packaging, and Labeling

Not applicable.

5.2.3 Product Storage and Stability

Not applicable.

5.2.4 Preparation

Not applicable.

5.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable.

5.4 Study Intervention Compliance

It is anticipated that participants in this study will occasionally miss or fail to complete an assessment or procedure, such as a completion of a rating scale or fail to complete a procedure within protocol-specified time frames due to equipment malfunction. Omissions such as these will be considered expected events and not protocol deviations provided they are infrequent and do not include data needed to assess safety or the primary study outcome. Cumulative proportions of these missed events will be monitored by the Investigators. If an individual misses more than 15% of the required assessments/procedures or if more than 15% of the participants miss completion of the same assessment or procedure, it will be considered a deviation. If they do not complete the computer task then the participant will be considered a withdrawal and we will not use their data. The source documents of the questionnaire, computer task data will be used to calculate study intervention compliance.

5.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Current use of medications that pass the blood brain barrier and act on histamine (i.e. diphenhydramine), dopamine (methylphenidate), norepinephrine (buproprion), serotonin (sertraline), or acetylcholine (amitryptiline) receptors will be exclusionary. Subjects will be excluded if they take these medications on a chronic basis. Subjects will be included if they have not taken the medication for five half-lives prior to a study visit.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 Discontinuation of Study Intervention

Discontinuation from the task will mean discontinuation from the study, and remaining study procedures will be stopped. Only clinical evaluations of AEs and follow up calls may occur following discontinuation. Any new clinically relevant finding will be reported as an adverse event (AE).
Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Completion of study intervention

- If any significant worsening of symptoms or active suicidal ideation, clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Concomitant medication use
- Investigator discretion
- Positive pregnancy test

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject has completed the study
- Death
- Screen Failure
- The reason for participant discontinuation or withdrawal from the study will be recorded in CRIS.

6.3 LOST TO FOLLOW-UP

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 SCREENING PROCEDURES

7.1.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

7.1.2 Screening activities performed after a consent for screening has been signed

Clinic:
Prior to consenting to the study, subjects will have undergone a screening under protocol 01-M-0254, “The Evaluation of Patients with Mood and Anxiety Disorders and Healthy Volunteers” or 17-M-0181 “Recruitment and Characterization of Research Volunteers for NIMH Intramural Studies” within 365 days of their enrollment in this study. Psychiatric history will be assessed using the SCID-I/NP (see First et al., 2001) using DSM-IV or DSM-5 diagnostic criteria.

Diagnostic eligibility (i.e., absence of current or past history of any DSM-IV or DSM-5 Axis I disorder) will have been determined prior to entry to the initial study according to DSM-IV or DSM-5 criteria and confirmed by the SCID-I/NP. We will require that all subjects have an updated physical examination and the following tests: physical exam, urine pregnancy test (for premenopausal women), and toxicology screening. A pregnancy test will be done in women of childbearing age who are not surgically sterile (i.e. bilateral oophorectomy, complete hysterectomy). Results of these tests will identify patients who should be excluded because of active medical problems or substance abuse that might affect clinical phenomenology or make participation in the protocol unsafe. Subjects are expected to meet all other inclusion and exclusion criteria to be eligible for study participation. Information obtained under the 01-M-0254 screening protocol or 17-M-0181 recruitment protocol may be used for research data in this protocol.

All screening tests and procedures must be performed within one year prior to enrollment, unless a time period is specifically mentioned.

7.2 EFFICACY ASSESSMENTS

7.2.1 Clinical Evaluations

Questionnaires:

State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983): 40-item scale assessing state anxiety (20 items) and trait anxiety (20 items).

- Anxiety Sensitivity Index (ASI;Reiss et al., 1986): 16-item scale assessing anxiety sensitivity in terms of the dispositional tendency to fear the somatic and cognitive symptoms of anxiety due to a belief that these symptoms may be dangerous or harmful.
- Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): 16 items assessing chronic, excessive, and uncontrollable worry.
- Intolerance of Uncertainty Scale short form (IUS-12; Carleton, Norton, & Asmundson, 2007): 12-item scale assessing reactions to impending uncertainty, ambiguous situations, and the future. It consists of two factors: prospective anxiety (7 items) and inhibitory anxiety (5 items).
- BIS/BAS scale (Carver et al., 1992):24 items assessing individual differences in the sensitivity of two motivational systems, the behavioral approach system (BAS) and a behavioral avoidance (or inhibition) system (BIS).
- Risk-taking behaviors scale (RTBS; Weber, Blais, & Betz, 2002): 14-item scale assessing people's willingness to engage in risky decision-making across different risk-taking domains including health/safety, recreation, ethics, social interaction, gambling.
- Positive Affect/Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988): 20-item scale assessing positive (10 items) and negative (10 items) affects.
- Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995): 11-item scale assessing personality/behavioral construct of impulsiveness.
- Sensation Seeking Scale (SSS) Form V (Zuckerman et al., 1978): 40-item scale assessing sensation seeking behaviors according to four dimensions associated with sensation seeking that are thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility.

Curiosity and Exploration Inventory (CEI-II) (Kashdan, T.B., et al.;2009): 10-item scale assessing individual differences in the recognition, pursuit, and integration of novel and challenging experiences and information.

7.2.2 Clinical Evaluations

Not applicable.

7.2.3 Biospecimen Evaluations

Not applicable.

7.2.4 Correlative Studies for Research/Pharmacokinetic Studies

Not applicable.

7.2.5 Samples for Genetic/Genomic Analysis

Not applicable.

7.3 Safety and Other Assessments

Not applicable.

7.4 Adverse Events and Serious Adverse Events

7.4.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

7.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.4.3 Classification of an Adverse Event

7.4.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

7.4.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

7.4.3.3 Expectedness

The LIP or Medical Associate Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.
All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.
The Principle Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.4.5 Adverse Event Reporting

Reportable events for this protocol will be tracked and reported in compliance with Policy 801.

7.4.6 Serious Adverse Event Reporting

Reportable events for this protocol will be tracked and reported in compliance with Policy 801.

7.4.7 Events of Special Interest

Not applicable.

7.4.8 Reporting of Pregnancy

Not applicable.

7.5 UNANTICIPATED PROBLEMS

7.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- 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

- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

7.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

7.5.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESIS

Multi-arm bandit: The two conditions in the multi-arm bandit are designed, in such a way that in one condition, purely value-driven exploration would result in the highest cumulative outcomes; whereas in the other condition, random exploration would be the optimal strategy. The primary null hypothesis for would be: *There is no significant scenario (1 vs. 2) x population (HV vs. AD) interaction* Additionally, the secondary null hypothesis would be: *There is no significant correlation between the difference of the exploration specific parameter and anxiety scores.*

8.2 SAMPLE SIZE DETERMINATION

Multi-arm bandit study

- Outcome measure used for calculations (almost always the primary variable): For the first behavioral experiment, the two conditions are designed to affect the nature of the optimal strategy, such that in one condition, the highest cumulative outcome depends on purely value-driven exploration; whereas, in the other condition, the best strategy involves adequate random exploration. From our pilot study, we know that there is a significant difference between scenarios in HV. Paired t-test p = 0.0014, tstat=3.5139, df=31, sd=13.4323.
- Test statistic: The model derived parameters will be analyzed using a 2-way repeated measures ANOVA, with the scenarios (experimental manipulation) and population (healthy volunteers, anxiety patients) being the 2 factors.
- Null hypotheses: There is no significant difference in model derived parameters between the 2 conditions and/or populations.
- Type I error rate (alpha): 0.05
- Power level: 80%
- Statistical method used to calculate the sample size, with a reference for it and for any software utilized: Repeated measure anova power analysis using R function wp.rmanova
- Anticipated impact of dropout rates, withdrawal: 10-15%
- Accrual rate and duration of study: The expected accrual rate is 2 participants a week. Thus, the total duration of each of our experiments is expected to be around 9 months.

Power analysis:
To run the power analysis, we use the R function wp.rmanova, with number of groups (Ng)=2, number of measurments (nm) = 2, Nonsphericity correction coefficient (Nscor)=1, Alpha = 0.05, power=0.8, Effect size (f) [Table below lists the sample size determined for different effect sizes.] We chose an effect size of f=0.35 and thus require a sample size of 66 subjects (33 HV and 33 AD). Given that we expect 15-20% of subjects to have bad EMG recordings, unanalyzable or small startle responses, or random choice probabilities, we will recruit a total of 80 subjects (40 HV, 40 AD)

N	F	Ng	nm	Nscor	Alpha	Power
198	0.2	2	2	1	0.05	0.8
89	0.3	2	2	1	0.05	0.8
66	**0.35**	**2**	**2**	**1**	**0.05**	**0.8**
51	0.4	2	2	1	0.05	0.8
33	0.5	2	2	1	0.05	0.8

8.3 POPULATIONS FOR ANALYSES

Multi-arm bandit study

- The subjects will be healthy adult male and female volunteers, ages 18-50. For each experiment there will be 2 groups, healthy controls, and anxiety patients
- The target number of completers for the clinic study will be N=40 per group for a total of 80 completers. Subjects who drop out will be replaced. The total accrual number for the clinic study will be 80 (see power analysis).

Pilot study
Pilot studies designed to test out additional stimulus parameters and factors underlying decision making will require additional participants. We plan to recruit up to 20 HV.

8.3.1 Evaluable for toxicity

Not applicable.

8.3.2 Evaluable for objective response

Not applicable.

8.3.3 Evaluable Non-Target Disease Response

Not applicable.

8.4 STATISTICAL ANALYSES

8.4.1 General Approach

- The main expected outcome measures are changes in the model derived parameters such as learning rate, exploration across conditions.

- Startle and performance data will be analyzed with ANOVAs, paired t-tests and other statistical tests as appropriate with significance levels set at 0.05
- For all parametric tests the appropriate checks on the distribution of the data will be performed prior to analysis.

8.4.2 Analysis of the Primary Endpoints

Clinic study:

- For the clinic experiment, the two conditions are designed to affect the nature of the optimal strategy. In one condition, the highest cumulative outcomes depend on purely value-driven exploration; whereas, in the other condition, the best strategy depends on random exploration. The model derived parameter (exploration inverse temperature) is one parameter that reflects the strategy used by the participant. In addition, another parameter of interest is the learning rate, which reflects the speed of learning based on prior trials.
- The model derived parameters follow an interval scale there is one data point per participant per condition.
- The difference in parameter estimates between the 2 conditions will be tested for significance using a paired t-test.
- The assumptions for the validity of a paired t-test: (1) The dependent variable must be continuous (interval/ratio). (2) The observations are independent of one another. (3) The dependent variable should be approximately normally distributed. (4) The dependent variable should not contain any outliers.
- Once we have a full sample (healthy volunteers and anxiety patients) the model derived parameters will be analyzed using a 2-way ANOVA, with the condition (experimental manipulation) and population (healthy volunteers, anxiety patients) being the 2 factors.

8.4.3 Analysis of the Secondary Endpoint(s)

- We expect this change in parameter estimates to be influenced by anxiety, that will be measured using potentiated startle and anxiety questionnaires.
- We expect this change in parameter estimates to be further influenced by the individual's reinforcement learning tendency, curiosity, exploration, sensation seeking, measured using self-reported questionnaires.
- The correlation coefficient between the difference in model derived parameters (between conditions) and the total scores and/or the total scores of the sub-scales of self-reported questionnaires will be computed.

8.4.4 Safety Analyses

Not applicable.

8.4.5 Baseline Descriptive Statistics

Not applicable.

8.4.6 Planned Interim Analyses

Not applicable.

8.4.7 Sub-Group Analyses

Not currently planned.

8.4.8 Tabulation of individual Participant Data

Not applicable.

8.4.9 Exploratory Analyses

Not applicable.

9 REGULATORY AND OPERATIONAL CONSIDERATIONS

9.1 INFORMED CONSENT PROCESS

9.1.1 Consent/Assent Procedures and Documentation

Study investigators designated as able to obtain consent are outlined in the KSP form. All study investigators obtaining informed consent have completed the NIMH HSPU 'Elements of Successful Informed Consent' training.
All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. Consent forms will be signed in the presence of a witness. Consent may be obtained in-person or using NIH-approved telehealth platforms.

The informed consent document will be provided as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomfort and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to any research activities taking place.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required.

Note: When required, the witness signature will be obtained similarly as described for the investigator and participant below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below.

When a hand signature on an electronic document is used for the documentation of consent, this study will use the following electronic platform to obtain the required signatures:

- iMedConsent platform (which is 21 CFR Part 11 compliant)

Both the investigator and the participant will sign the electronic document using a finger, stylus or mouse. Electronic signatures (i.e., the "signature" and a timestamp are digitally generated) will not be used.

9.1.2 Consent for minors when they reach the age of majority

Not applicable.

9.1.3 Considerations for Consent of NIH staff, or family members of study team members

Consent for NIH staff will be obtained as detailed above with following additional protections: Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service in order to minimize the risk of undue pressure on the staff member.

9.1.4 Consent of Subjects who are, or become, decisionally impaired

Consent is obtained the day of the study visit. Participants who are decisionally impaired are excluded and subjects would not become decisionally impaired during the time frame of the single, outpatient study visit.

9.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data (including demographics information and clinical rating scales), which is for purposes of statistical analysis and scientific reporting, will be transmitted in a HIPAA compliant manner and securely stored in the Clinical Trials Data Base (CTDB) sponsored by NICHD. Individual participants whether they have been in a NIH study before or not, and their research data will be identified by a unique study identification (ID) number. The study data entry and study management systems used by CTDB will be secured and password protected. All study investigators will have access to data in CTDB with different level of access, e.g. data entry, reporting. Electronic data (including imaging data) and electronic personally-identifiable health information (ePHI) will be stored on secure servers within the NIH firewall with access for study personnel only.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

9.4 FUTURE USE OF STORED SPECIMENS AND DATA

No specimens are collected. Data will be de-identified and stored at the clinical site for an indeterminate period of time so that they could be used in future studies and shared for collaboration with other researchers. Data from structured diagnostic interviews and symptom ratings are kept in secure research files and electronically on the Branch server space or within the CTDB database. Clinical data will be entered into CRIS and therefore will go into BTRIS. Biophysiological data will be stored electronically on the Branch server space. De-identified data

may be submitted to open-access repositories for secondary research. A code, which will be kept by the study team on a password and firewalled server and/or in a locked file cabinet, will link de-identified data and samples to clinical and demographic information. Participants will provide informed consent for this use.

9.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI and research team and the NIMH Office of Regulatory Oversight (ORO).

9.6 CLINICAL MONITORING

As per ICH-GCP 5.18 clinical protocols are required to be adequately monitored. Monitoring for the NIH site will be conducted according to the "NIMH Intramural Program Guidelines for Monitoring of Clinical Trials". Monitors under contract to the NIMH OCD ORO will visit the NIH site to monitor aspects of the study in accordance with the appropriate regulations, policies and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information from clinical databases (e.g. CTDB) with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site study files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), NIH, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, clinical database records and pertinent hospital/sources or clinical records readily available for inspection by the local IRB, OHRP, the site monitors, as applicable and the NIMH staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and applicable regulatory obligations.

9.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.
Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.
Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference

on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.8 DATA HANDLING AND RECORD KEEPING

Data Collection and Management Responsibilities
Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.
Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.
Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Clinical Research Information System (CRIS), a 21 CFR Part 11-compliant data capture system provided by the Clinical Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.8.1 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, and as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.9 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to National Institute of Mental Health Clinical Director. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

9.10 PUBLICATION AND DATA SHARING POLICY

9.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:
National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers two years after the completion of the primary endpoint by contacting Dr. Christian Grillon.

9.10.2 Genomic Data Sharing Plan

This protocol is not subject to the Genomic Data Sharing (GDS) Policy.

9.11 COLLABORATIVE AGREEMENTS

Not applicable.

9.11.1 Agreement Type

Not applicable.

9.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute of Mental Health has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections

PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

11 REFERENCES

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