Computer-Based Treatment for Social Anxiety Disorder

NCT03415022

Study Protocol and Statistical Analysis Plan

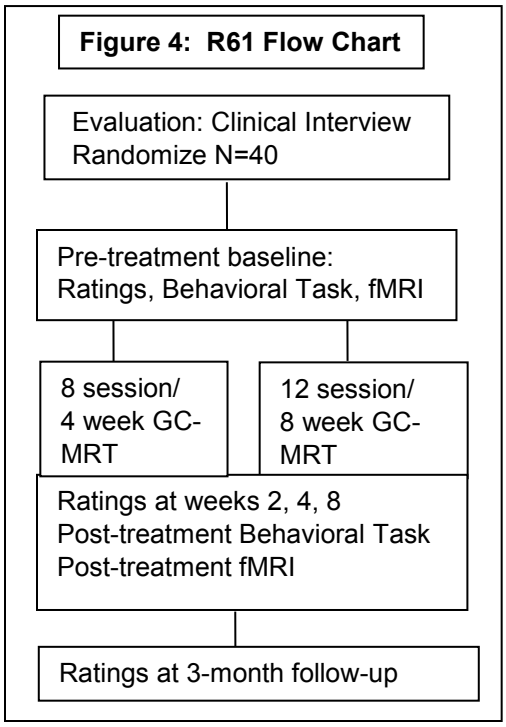
Version Date: July 21, 2020

3.3. C. Research Design and Methods: R61 Phase.

3.3. C.1. Overview. The R61 Phase is designed to clarify engagement of the attention allocation target, to optimize dosage of GC-MRT (RCT comparing 8 vs. 12 sessions), and to explore whether the treatment engages two processes influencing attention allocation: disengagement from threat, and social reward.

3.3. C.2. R61 Method: Patients: The goal is to enroll a sample with clinically significant SAD, using few exclusion criteria to maximize generalizability. Patients will be obtained by clinical referral and recruitment notices posted online and locally. Forty adults age 18-60 with clinically significant SAD, as assessed by MINI structured interview and self-rated Liebowitz Social Anxiety Scale (LSAS-SR) total ≥50, will enter the study after psychiatric clinical evaluation, including and Hamilton Rating Scale for Depression (HRSD). The LSAS cutoff score was chosen for optimal balance between diagnostic specificity and sensitivity for SAD.[80] Key exclusion criteria will be at least moderately severe depression (HDRS 17-item score >20), indicating greater need for non-experimental treatment; substance use disorder in the past 30 days (other than nicotine, or mild alcohol or cannabis abuse); bipolar or psychotic disorders; acute suicidal ideation (assessed by Columbia Suicide Severity Rating scale, CSSR); other unstable psychiatric, neurological, or medical conditions that could interfere with study participation or interpretation of outcomes; contraindication to MRI. (see Human Subjects for details).

The self-rated version of the LSAS will be used only at screening for eligibility assessment. The clinician-rated LSAS will be the primary outcome measure, assessed at baseline, during treatment, and post-treatment. Using the self-rated LSAS at screening avoids the bias that reportedly can occur when the primary outcome measure is the basis for an entry cutoff criterion, as raters could feel pressured to maximize baseline scores to meet the cutoff, thus distorting outcomes.



3.3. C.3 R61 Intervention: Patients will be randomized to 8 biweekly sessions of GC-MRT over 4 weeks vs. 12 sessions of GC-MRT over 8 weeks (8 biweekly, then 4 weekly), using GC-MRT as described above in the preliminary study,[13] but without a control treatment – all R61 patients will receive active GC-MRT.

Training sessions of 20 min. will use the Eye-Link 1000 plus eye-tracker running Experiment Builder software (SR Research, Kanata, Ontario, Canada). Before each training session patients will be told that background music will accompany the session. Staff will provide a music menu and ask the patient to choose music he or she would like to hear during the session. Each training session begins with a 9-point gaze calibration, followed by 9-point validation, yielding reference data needed for computing gaze positions. Calibration will be repeated if visual deviation is >0.5 degrees on the X or Y axis, and training will begin only when calibration parameters are achieved. Operating distance to the eye-tracking monitor will be 70 cm. The stimuli will be presented on a monitor with 1920×1080 pixel resolution. Patients will be asked to view each face matrix freely in any way they choose, without additional instruction. GC-MRT group patients who inquire about the interruptions in music will be told that everything is working properly and to continue to view the stimuli. Independent evaluators will not be aware of session-scheduling nor observe training sessions, which will be held in a remote room. Patients will be told to refrain from discussing their training session experiences during clinical assessments.

3.3. C.4 Assessments :

These will include eye tracking of attention allocation during GC-MRT, self-ratings, clinician ratings (by an independent evaluator blind to GC-MRT dose assignment and scheduling of GC-MRT sessions), computer-based behavioral tasks, and MRI. Attention allocation will be assessed at every GC-MRT session. MRI assessments and behavioral tasks will be conducted pre- and post-treatment. All other outcome assessments will be conducted at baseline and at weeks 2, 4, and 8, and 3 months later (3-month follow-up).

3.3. C.4.a. Primary Outcome Assessment for Target of Attention Allocation: The primary outcome measure will be defined as % dwell time on threat faces (dwell time on threat faces/dwell time on all faces), derived from eye-tracking data obtained throughout each treatment session. Fixations will be defined as ≥100 ms of stable fixation within 1º visual angle. For each matrix we will define two Areas of Interest (AOI's), one of the eight disgust facial expressions (i.e., the threat AOI) and one of the eight neutral facial expressions (the neutral AOI). Attention allocation to threat will be measured by computing total dwell time in milliseconds per defined AOI and calculating the proportion of dwell time on the threat AOI relative to total dwell time on both AOI's, thus reflecting gaze allocation to threat stimuli. Percentage of dwell time on threat AOI across the 30 presented matrices for each session will be averaged for a final score of attention allocation to threat per session. As in the pilot study, to derive baseline % dwell time we will average the percentage of dwell time on threat AOI during the first five matrices presented in Session 1, as gaze-contingency learning has been shown to be minimal at this early stage.[13]

3.3. C.4.b. fMRI Tasks: Patients will complete MRI twice (pre-treatment and post-treatment) using tasks that have been previously shown to differentiate SAD from control participants. Resting state data will be obtained for 15 minutes prior to task completion.

Attention control task: The Emotional Faces Shifting Attention task[72] (EFSAT) will be used to assess distraction of attention by threat faces. EFSAT stimuli are comprised of a trio of geometric shapes (circles, rectangles, triangles) alongside a trio of faces within the same field of view. For “Match Faces,” participants select one of two bottom faces (neutral vs. emotional) matching the emotion of the top target face. “Match Shapes” will have similar instructions, to select one of two bottom shapes that matches the top shape. Face stimuli are from a validated stimulus set,[81] the identities always differ, and equal numbers of male and female faces are presented. The paradigm comprises 36 blocks: 18 blocks of matching shapes interleaved with 18 blocks of matching emotional faces, counterbalanced across two runs. Each target face condition (angry, fear, happy) is presented for an entire block six times without repetition. Each 20s ”task” block contains four sequential matching trials, 4s each, preceded by a 4s instruction image to either “Match Faces” (attend to faces) or “Match Shapes” (attend away from faces). Participants respond by pressing response buttons. Stimuli will be presented using presentation software (Neurobehavioral Systems).

Social Incentive Delay task:[66] This social reward version of the Monetary Incentive Delay task[75] was developed to assess social and monetary reward processing. We will use the social reward processing runs of this task. Participants are informed that pictures of neutral faces will be presented as rewards for successful trials. Each of 3 runs are ”win versions” (i.e., faces can be won or not won, but cannot be lost). Trial ”wins” result in the presentation of a static image of a face with a neutral expression (closed mouth images selected from the NimStim set of facial expressions).[82] Runs begin with a 10s instructional screen.

Each trial includes: (i) a 2000ms cue indicating whether adequately quick responses to the bulls-eye would result in a ‘win’ (a triangle) or not (a circle); (ii) a 2000–2500ms crosshair fixation; (iii) a target bulls-eye presented for up to 500ms that requires a speeded button press; (iv) 3000ms of feedback that indicates whether that trial is a ‘win’ or not, with wins accompanied by an image of a face and (v) a variable length inter-trial interval crosshair such that the total duration of each trial is 12s. Trial types (i.e., potential win or no potential win) are aperiodic and pseudorandomly ordered. Each 8 min run contains 40 trials, of which 20 are potential win trials. During each run, participants view a face image reward if responses to the bulls-eye are adequately quick. Coincident with feedback, cumulative win totals are presented. Participants will be instructed to respond to all target bulls-eyes as quickly as possible to win on as many trials as possible, and win or non-win outcomes are contingent on reaction times. The task is adaptive such that participants are successful on two-thirds of trials, regardless of individual differences in reaction times. Prior to scanning, participants rate face stimuli on the dimensions of valence and arousal. Stimuli will be presented using E-Prime presentation software version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA).

3.3. C.4.c. Behavioral Task Assessments

Attention Control Task: (see EFSAT 3.3. C.4.c. above) This will assess reaction times for matching shapes alongside happy versus angry distractors.

Probabilistic Social Reward Learning Task**:**[56,66] This 25-min task is presented using E-Prime (version 1.1; Psychology Software Tools, Inc, Pittsburgh, PA). Subjects press a button to indicate whether a short (11.5 mm) or a long (13 mm) mouth appeared on a previously mouthless cartoon face. The task includes three blocks of 100 trials. Within each block, an equal number of short and long mouths appear for 100 ms each.[77]The difference between mouth sizes as well as the duration of stimulus exposure is small, providing an ideal experimental setting for a response bias to develop without risk of inducing performance at chance level.[84]

Using an asymmetric reinforcer ratio elicits a response bias.[83,84] Correct identification of either the short or long mouth is rewarded (by a video clip of smiling actor with thumbs up sign) three times more frequently (“rich stimulus”) than correct identification of the other mouth (“lean stimulus”). The reinforcement allocation and key presses are counterbalanced across subjects. In each block, only 40 correct trials (30 rich, 10 lean) are

rewarded, so each subject is exposed to the same reward ratio. Subjects are informed that the purpose of this task is to win as much money as possible, and that not all correct response will receive a reward feedback; but they will be unaware of the disproportionate reward for one of the stimuli.

3.3. C.4.d. Diagnostic and Clinical Rating Assessments
Raters (MD or PhD level) experienced with the assessment of SAD will conduct clinician assessments. Independent evaluators blind to randomization assignment will conduct the primary symptom severity outcome measure (LSAS) and other outcomes. Reliability will be established by joint ratings prior to study initiation and repeated at 6-month intervals during the study to minimize drift.

MINI International Neuropsychiatric Interview (MINI,[85] screening only). This structured diagnostic interview will establish DSM-5 diagnoses for eligibility assessment.
Liebowitz Social Anxiety Scale – Self-Rated (LSAS-SR,[86] screening only) 24-item self-rated assessment of social anxiety symptom severity, well validated.
Hamilton Rating Scale for Depression, 17-item (HRSD,[87] screening and weeks 0,2,4,8, 3-month follow-up)
Columbia Suicide Severity Scale[88] (screening and as-needed) will be used for screening and to assess an suicidal ideation occurring during participation.

Outcome measures at weeks 0,2,4,8, 3-month follow-up:
Liebowitz Social Anxiety Scale – Clinician-Rated (LSAS)[14,89] Widely used and well validated 24-item assessment of severity of symptoms of SAD.
Social Phobia Inventory (SPIN)[90] **–** Validated self-rating assessment of severity of symptoms of SAD.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ)[15] – Self-rated scale for quality of life.
Revised Social Anhedonia Scale[91] – 15-item self-rated scale derived from Chapman Social Anhedonia Scale, with superior discrimination of social anhedonia from social anxiety.
Post-treatment Debriefing Questionnaire – This self-rated form will assess the participant's experience of GC-MRT, including treatment acceptability (using a modified version of the **Client Satisfaction Questionnaire**)[92], and awareness of the reward contingency.

Randomization Method (R61 and R33). We will use stratified randomization to assign subjects into two randomized groups. Strata will be defined based on baseline medication use (yes/no). Forty subjects will be randomized in the R61 phase to two dosage groups,

3.3. C.5 Data Analysis and Hypothesis Testing
All quantitative measures will be graphed by group and checked for outliers and inconsistent values. If a variable has many outliers or shows heteroscedastic behavior (i.e., unequal variances), we shall consider transformations using a power function. Any remaining outliers will be winsorized (i.e., censored down to the nearest non-outlier value). Missing values. Missing values on outcome measures will be summarized by randomization group. We will test for differential missingness between groups. We will use mixed effect models for the statistical analyses, as these can analyze data with ignorable missingness (missing at random). G*Power 3.1. and the R library longpower[93,94] were used to calculate statistical power.

R61. Forty adults with SAD will be randomized to standard GC-MRT (8 sessions in 4 weeks) or extended GC-MRT (8 sessions in 12 weeks), with the target of attention allocation assessed at each session. ***Aim 1:*** *Hypothesis 1: The target measure (% dwell time on threat faces) will decrease significantly during GC-MRT.* The primary analysis will be intention-to-treat using a mixed effect model with change in % dwell time from baseline to the repeatedly measured outcome from all sessions after session 3 in both groups, using categorical time and baseline % dwell time as fixed effects, with an AR(1) correlation structure within subjects. The effect of interest will be the intercept, as this is a pooled analysis that does not differentiate between randomization groups or time points. A secondary analysis will use data from all sessions to test the categorical time effect predictor's effect, to identify time points with significant mean change scores adjusting for baseline medication use (yes/no). Additionally, the completer analysis will be a matched pair t-test of pre-post % dwell time values. Power Analysis: For the completer analysis, our already published data lead us to expect an effect size for reduction in the % dwell time of at least Cohen's d = 0.68. Assuming a 10% dropout with N=40 enrolled subjects, and a 0.05 significance level, we will have at least 98% power to detect this change, with d = 0.48 the minimum detectable effect size. For the repeated measures analysis, with within-subject autocorrelation parameter r = 0.6, we will have at least 80% power to detect an effect size of f = 0.17,

corresponding to *d* = 0.34, while with r = 0.2, the minimal detectable effect size is f = 0.23 or *d* = 0.45. In either case, the power for *d* = 0.68 will be >99%.

Aim 2: Hypothesis 2: *Eight weeks after starting treatment, mean Liebowitz Social Anxiety Scale (LSAS) total score will be significantly lower in the 8-week treatment group than in the 4-week group.* We will use a t-test for the change score at 8 weeks after starting treatment for completers. We will also compare groups on % dwell time at last session but do not expect a group difference. Power Analysis. We do not have preliminary data for the 8-week dose of treatment. For the two-group t-test, with n=20 per group enrolled, and 18 per group completers (10% dropout), we will have 80% power to detect an effect of size d=0.96 or larger. Thus we will be able to detect large effect sizes for the dosage difference**.** However, dose selection for the R33 will not require statistically significant superiority (see criterion for selecting dose, below).

Aim 3 (Exploratory): (See below for processing MRI and tasks data) We will test the association between change in attention control and reward processing and change in % dwell time by Pearson correlation coefficients. *We will also explore predictors of target engagement (baseline attention allocation and neural activation), to advance personalized treatment.* We will fit mixed effect regression models as described in Hyp 1, with repeatedly measured reduction in % dwell time as outcomes, with the predictors listed above.

R61 Go-Nogo Criterion: Mean % dwell time on threat faces during the last session of the 8-session or 12-session treatment will decrease by more than 7.2 percentage points relative to baseline, corresponding to a medium effect size of Cohen's d=0.48, based on preliminary data. We have >80% power to detect this difference under all scenarios. Clinical significance of cutoff: Based on preliminary data, since % dwell time reduction will partially mediate clinical symptom reduction, this effect corresponds to symptom reduction of d = 1.34, corresponding to 21.3 points on the LSAS scale. **R61 criterion for selecting dose for the R33:** If only one dosage group passes the Go-Nogo Criterion, that dose will be selected for the R33. If both dosage groups satisfy the Go-Nogo Criterion, we will decide based on the following: If improvement (decrease) in LSAS total score 8 weeks after starting treatment is at least 7 points greater in the 12-session/8-week treatment group than in the 8-session/ 4-week treatment group, we will use the 8-session/12-week treatment in the R33.

Aim 4*: Hypothesis 3: Compared to control treatment, GC-MRT will significantly improve symptoms (LSAS) & QoL (Quality of Life Enjoyment & Satisfaction Scale, QLESQ: a) at post-treatment and b) at 3-month follow-up.* As primary analysis, we will use a two-sample t-test for the LSAS change scores at the last session in completer subjects. For the 3-month follow-up, a similar analysis will be performed. Secondary analysis will be similar analyses of the QLESQ, and a mixed effects model of each outcome with change score (relative to baseline) as the outcome, and randomization group, time point, and the baseline score as the predictors. Power Analysis. We assume 10% drop-out in each group. From our preliminary data analysis, expected effect size for reduction in LSAS for completer subjects, compared to controls, will be *d* = 1.35. Using a two-sample t-test, with Bonferroni-corrected 0.025 significance level, we will have 99% power to detect this. We do not have preliminary data for the QLESQ; the minimal detectable effect size for the change difference will be d=0.74, a moderate effect size.

Hypothesis 4: *After GC-MRT, change in % dwell time post-treatment will be significantly associated with improvement in LSAS and QLESQ totals at post-treatment and at 3-month follow-up.* We will calculate Pearson correlation coefficients between % dwell time reduction and LSAS reduction, and, separately, for % dwell time and QLESQ reductions. Power Analysis. From our preliminary data analysis, the expected correlation coefficient for the reduction in % dwell time and reduction in LSAS will be r > 0.32. With n = 80 subjects and 10% dropout, we will have 80% power to detect a Pearson correlation of r = 0.32 at the 0.05 level.

Aim 5 (Exploratory): *To assess whether attention control and reward processing predict symptom change (using same assessment methods as in Aim 3), with fMRI done pre- and post-treatment in a subset (n=60).* We will fit regression models, with LSAS change relative to baseline as outcome, and with the baseline predictors listed above as fixed effects, Moderation relationships of treatment effect for the baseline predictors will be explored by including interaction terms with randomization group. We will test the association between change in attention control and reward processing and change in symptoms by Pearson correlation coefficients.

fMRI Data Acquisition: Prior to scanning, patients will practice all tasks and gain familiarity with the scanning environment. Foam pads securing patients in the head coil will limit head movement during data acquisition. The MRI component will last approximately one hour and 15 minutes, using a 3T General Electric MR750 (GE Medical Systems, Waukesha, WI, USA) located in NYSPI, and equipped with a 32 channel receive-only head coil. At the beginning of each session, 15 minutes resting state data will be collected to explore connectivity

patterns within reward and attention control brain regions. We will acquire functional T2*-weighted echo-planar images (EPIs) depicting the blood-oxygen-level-dependent (BOLD) contrast (Repetition time: 2300 ms, echo time: 23 ms, flip angle: 90º). Whole brain acquisitions will consist of 30 sagittally oriented slices of 3.5mm thickness and 1.7x1.7mm2 in-plane resolution (matrix: 128x128, field of view: 22 cm). The first six EPI volumes in each run will be discarded to avoid T1 equilibrium effects. High-resolution T1-weighted magnetization prepared rapid acquisition gradient-echo sequence will be obtained to serve as anatomical reference.

fMRI Data Preprocessing: Statistical Parametric Mapping (SPM12) software package (Wellcome Trust Centre for Neuroimaging, London; www.fil.ion.ucl.ac.uk/spm)[95] will be used for image processing steps. During preprocessing, images will be temporally corrected to account for differences in slice time collection, spatially realigned to the first image of the first run, normalized to a Montreal Neurological Institute (MNI) template, and smoothed with an 8 mm isotropic Gaussian kernel. Additionally, subjects with more than 3mm of head motion in any dimension from one EPI brain volume to the next will be removed from analysis.

Attention Control Task fMRI**:** Blocks of Match Faces (shapes in background) and Match Shapes (faces in background) will be modeled with 6 box-car regressors separately based on target emotion or shape (angry, fearful, or happy/ circle, square, or triangle), and effects will be estimated at each voxel for each participant and taken to the second level for random effects analysis. In addition, six movement parameters obtained during realignment will be included in the model as regressors to account for motion-related effects in BOLD signal.

Whole-brain 2X2 voxel-wise Analysis of Variance (ANOVA) will be conducted to evaluate main effects of Time (pre- and post- treatment), Stimuli type (match faces and match shapes), and Time by Emotion interactions for only angry faces at the R61 phase for each dose group. For the R33 phase, whole-brain 2X2X2 ANOVA will be conducted to evaluate main effects of Group (active and control), Time (pre- and post-treatment), and Stimuli type (match faces and match shapes), and Group by Time by Stimuli type interactions for only angry faces. A stringent threshold for significance will be set at $p<0.05$, corrected for multiple comparisons across the entire brain using a FWE with a cluster size of at least 10 contiguous voxels. Significant main effects and interactions will be tested by post hoc t-tests to clarify the direction of effects.

Reward Task fMRI: During individual-level analyses, functional activation maps of the reward task will be computed by regressing each voxel's fMRI response time course onto an ideal response function consisting of a canonical hemodynamic response function convolved with the time-series of each response type of the entire duration of anticipation and outcome phases of the task. In addition, six movement parameters obtained during realignment were included in the model as regressors to account for motion-related effects in BOLD signal.

A whole-brain voxel-wise two-way t-test model will be conducted with two time points (pre-, post-treatment) in the R61 phase for each dose group. It will be applied separately for the anticipatory and outcome phases of the task, and each outcome will be modeled against an implicit baseline (the anticipatory phase models only 'potential win' trials and the outcome phase models only successful 'potential win' trials). For the R33 phase, whole-brain 2X2 ANOVA will be conducted to evaluate main effects of Group (active and control), and Time (pre- and post- treatment), and Group by Time interactions. Significant clusters will be further evaluated by extracting subject- and condition-specific signal intensity coefficients to evaluate simple effects.

Resting State Analysis**:** We will apply probabilistic independent component analysis (PICA) using the Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) toolbox of the FMRIB Software Library (FSL) package. A temporal concatenation tool in MELODIC will derive group level components across all subjects. The number of dimensions will be estimated using the Laplace approximation to the Bayesian evidence of the model order. The whitened observations will be decomposed into sets of vectors that describe signal variation across the temporal domain (time-courses) and across the spatial domain (maps) by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique. These functional connectivity component maps will be standardized into z statistic images via a normalized mixture model fit, thresholded at $z>5$. Networks of interests including the reward network, salience network, executive control network, and the default mode network will be identified by visual inspection. The between-subject analysis will be carried out using dual regression, a regression technique that back-reconstructs each group level component map at the individual subject level).[96]

Voxel-wise two-sample t-tests will be used to assess statistically significant differences in FC between the groups using a 5000 non-parametric permutation testing. A threshold-free cluster enhanced technique will control for multiple comparisons. This method allows detecting significant clusters without having to define cluster size or the number of clusters prior to analysis. Resulting statistical maps will be thresholded at $p<0.05$ family-wise error (FWE)-corrected for multiple comparisons. The Harvard-Oxford atlases incorporated in FSL will be used to identify the anatomical regions of the resulting PICA maps.

Attention Control Task behavioral analysis: The accuracy of trials and the RTs for accurate trials will be recorded. Behavioral data will be submitted to a 2 Time (pre-, post- treatment) x 2 Stimuli type (match faces and match shapes) ANOVA for angry faces only in the R61 phase for each dose group. For the R33 phase,

behavioral data will be submitted to a 2 Group (active and control) X 2 Time (pre-, post- treatment) x 2 Stimuli type (match faces and match shapes) ANOVA for angry faces only. Significant main effects and interactions will be followed up with two-tailed t-tests, $p < 0.05$.

Reward Task behavioral analysis: Valence, arousal ratings of faces, and reaction times (RTs) for both potential reward and non-potential reward trials will be recorded. RTs, valence and arousal ratings of faces will be submitted to 2-way t-tests (pre-, post-treatment) for the R61 phase for each dose group. For the R33 phase, a two-way ANOVA will be conducted to test main effects of Group (control and treatment), Time (pre- and post-treatment), and Group by Time interactions. Interactions will be followed up with two-tailed t-tests, $p < 0.05$.

Social Probabilistic Reward Task: Response bias (log *b*; primary variable) and discriminability (log *d*; control variable) will be computed following prior procedures.[77,83,97] using the following formulas:

$$\log b = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}}\right) \qquad \log d = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}}\right)$$

Response bias indexes the systematic preference for the response paired with the more frequent reward ("rich stimulus"), or the extent to which behavior is modulated by reinforcement history. A high response bias emerges when subjects show high rates of correct identification (hits) for the rich stimulus and high miss rates for the lean stimulus (i.e., the stimulus associated with less frequent rewards). To examine general task performance, secondary analyses will consider hit rates scores (% correct responses), RT, and discriminability. Discriminability assesses the subjects' ability to perceptually distinguish between the two stimuli, and thus can be used as a proxy of task difficulty.

Data Reduction: The main dependent variable for the PRT will be Reward Learning, operationalized as the increase in response bias during the final block relative to the first block [Reward Learning =ΔResponse Bias = Response Bias(Block 3) - Response Bias(Block 1)]. ΔResponse Bias is consistently positive in healthy subjects, and we selected this as the main outcome measure because lower values of it have been linked to current and future anhedonic symptoms[77,78,98] and reward-related cortico-striatal activation.[99]

PROTECTION OF HUMAN SUBJECTS

a. **Human Subjects Involvement, Characteristics, and Design**
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Overview:

We anticipate recruiting and entering 40 adults, age 18-60, with social anxiety disorder. They will complete diagnostic evaluations and begin full testing, including procedures of behavioral tasks, MRI, and 8 or 12 sessions of computer-based treatment. We estimate that overall 10% of participants will not complete all procedures due to noncompliance or movement artifacts**.**

Screening:

Outpatients with social anxiety disorder (meeting diagnostic criteria on MINI structured interview, and with self-rated Liebowitz Social Anxiety Scale total score ≥ 50) will be recruited by advertisements, postings, and clinician referrals, and will be screened for participation in the NYSPI Anxiety Disorders Clinic.

Informed Consent:

The voluntary nature of the study, the nature and the risks of the procedures, the amount of financial remuneration for participating in the study, and alternatives to participating in the study will be discussed with each subject prior to obtaining written informed consent.

Inclusion Criteria

1) Either gender and all ethnic and racial groups;
2) Age 18 - 60;
3) Diagnosis of social anxiety disorder
4) Total score of ≥50 on self-rated Liebowitz Social Anxiety Scale (LSAS-SR)
5) Able to provide informed consent.

Exclusion criteria

1) Lifetime diagnosis of any psychotic disorder, bipolar disorder, or mental retardation.
2) Depression of moderate or greater severity as assessed by 17-item Hamilton Rating Scale for Depression score of >20.
3) Serious suicidal risk or history of violent behavior which would make participation in the protocol unsafe (assessed with the Columbia Suicide Severity Scale).
4) Severe alcohol or cannabis use disorder in the prior three months, or any severity of other substance use disorder in the prior three months (except nicotine use disorder), as evidenced by history or urine toxicology screen;
5) Women who are pregnant or who are not using an effective birth control method.
6) Any medical or neurological problem that might affect interpretation of findings or safety of participation (e.g., malignancy, neurological diseases of the brain).
7) Any medical or neurological condition that might affect safety of undergoing MRI (heart pacemaker or metal in the body, e.g., shrapnel, bullets, surgical prostheses or surgical clips)
8) Any psychotropic medication treatment in the past 4 weeks except for serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor at stable dose for 3 months, confirmed by treating clinician.
9) Any current psychotherapy for SAD.