Project IMPACT: In-the-Moment Protection From Automatic Capture by Trigger

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1.0 Specific Aims (from grant)

In response to PAR-14-051, Mechanisms of Behavior Change in the Treatment of Alcohol Use Disorders, this application: "Project IMPACT: In-the-Moment Protection from Automatic Capture by Triggers," proposes to translate new scientific knowledge about the baroreflex (BAR) to better understand its role in drinking behavior change. The BAR is an automatic physiological mechanism that maintains continuous communication between the heart and brain, and can be assessed by neurocardiac signals such as heart rate variability (HRV). It is linked to regulation of emotional arousal and cognitive control of behavior, aspects of behavioral flexibility emphasized in many empirically supported behavioral alcohol use disorder (AUD) treatments. The BAR affects behavior change directly by influencing attention capture, arousal, and involuntary visceral reactions to cues and indirectly by interfering with, or enhancing, conscious intentions and cognitive effort. The BAR also both negatively affects, and is negatively affected by, alcohol use as well as drugs, depression, anxiety, and trauma, suggesting its broad involvement in biobehavioral disorders.

Clinical and experimental research supports the translational significance of the BAR mechanism for AUD intervention. Neurocardiac signaling spontaneously improves during and following behavioral treatment for AUD. Increased BAR sensitivity predicted better drinking outcomes. Thus, the BAR mechanism participates in the natural biobehavioral processes of recovery. Further, neurocardiac signaling and BAR sensitivity can be experimentally manipulated using simple behavioral breathing techniques such as resonance breathing and HRV biofeedback. These techniques lead to enhanced neurocardiac signaling and relatively immediate arousal modulation, decreased anxiety, and enhanced cognitive functioning in anticipation of, or during, induced stress. Thus, direct BAR manipulation may increase the rate and/or extent of neurocardiac recovery during AUD treatment. Finally, using data from a single 5-min period of resonance breathing, the BAR mechanism was computationally modeled and underlying biological change processes (cardiac muscle, vascular dynamics, and afferent neural traffic) were identified, as well as the subset of persons who showed neurocardiac improvement, suggesting a novel approach to subtyping and client-treatment matching. Three aims are proposed to understand the role of the BAR mechanism in positive behavior change when triggers that can instigate relapse are encountered, to characterize BAR-mediated change at multiple system levels, and to identify how and for whom the BAR mechanism is linked to control of drinking behavior.

Specific Aim 1: To determine whether strategic manipulation of the BAR mechanism "in the moment" bolsters treatment gains. Women (mothers of young children) in treatment as usual (TAU, 12-wk community-based, empirically supported, behavioral outpatient addiction treatment) will be randomly assigned to receive a BAR or placebo intervention. The BAR intervention will use an existing iPhone resonance breathing application ("app"); the placebo intervention will use the app at a normal breathing frequency that does not influence the BAR. Clients will be taught to use the apps in their daily lives (outside the context of treatment) when they anticipate or encounter risky emotions and situations. Beyond the effects of TAU, it is hypothesized that the BAR versus placebo intervention will lead to better alcohol and drug use outcomes and reduced anxiety, depression, and craving.

Specific Aim 2: To examine naturalistic (placebo) and manipulated (active intervention) changes in underlying physiological and neurobiological control systems. All experimental participants (Aim 1) will complete a laboratory session pre- and post-intervention (i.e., pre-post app use) to precisely assess level and change in HRV, BAR sensitivity, and neurocardiac connectivity. Based on previous findings, we predict BAR improvement in both groups as the result of general health improvements associated with treatment. We further predict that the BAR intervention will instigate significantly greater improvements in HRV and BAR sensitivity as well as improved neurocardiac (fMRI-ECG) connectivity compared to placebo.

Specific Aim 3: To characterize how and for whom the BAR mechanism affects change holistically. The BAR mechanism will be modeled individually for each participant with a computational physiology approach and 5 min of resonance breathing data from Aim 2. We posit that the BAR mechanism supports behavior change by influencing multiple interacting biological systems and that it will operate differently across people. Thus, we predict that computational modeling of the pre-treatment lab session data will enable us to forecast who the BAR intervention is most likely to benefit. Further, we predict that our model will reveal a specific pattern of underlying and unobservable cardiac, vascular, neural change resulting from BAR intervention that will parallel sustained positive treatment gains and thus capture the biological processes that support how an automatic physiological mechanism affects behavior change. We will elaborate the model using the behavioral data (Aim 1) and genetic data (exploratory) to understand how the BAR mechanism propagates change at multiple system levels.

2.0 Research Design (Updated IRB approval 7/24/19)

A. Research Procedure Overview

Women who are receiving outpatient substance abuse treatment at the Center for Great Expectations (CGE) will be recruited during Treatment Week 2 after group therapy sessions by a trained clinical research staff. All participants will receive a structured clinical interview (SCID), to verify CGE diagnoses. Women will be randomized into treatment as usual (TAU) plus resonance breathing (+RB) or TAU plus an active, control condition (+CON).

Recruitment and Baseline Phase. Starting with Treatment Week 2 (to ensure client engagement in treatment), participants individually will asked to complete a battery of surveys related to levels of anxiety, depression, alcohol/drug triggers, an assessment of trauma, health and demographic information, and information related to social circles. Any alcohol or drug use that occurred during the three months prior to treatment will also be recorded using a Timeline Follow Back approach and compared to weekly drug testing results performed by CGE.

Randomization into intervention and control groups. Urn randomization will be used to assign participants to the two groups to maximize the probability that the groups will be balanced with regard to important prognostic characteristics and to preserve unpredictability/allocation concealment. Variables that will be used as indicators of critical prognostic characteristics include age due to its substantial influence on neurocardiac signaling, and diagnosis of AUD, consistent with our primary focus on drinking behavior change.

Intervention Phase. In Treatment Week 4, all participants will complete Lab Session 1 (described below) and then be given an iPhone without a phone/data contract. TAU+RB participants' phones will be pre-loaded with a resonance breathing app set at 6 breaths per minute, and they will receive training on how to perform slow breathing without hyperventilating and how to use the breathing app on the iPhone. TAU+CON participants' phone will be pre-loaded with the same app set to a paced breathing rate of 14 breaths per minute (a rate closest to the normal average breathing rate). Participants in the TAU+CON group will receive the same training on how to use the app as the TAU+RB group.Clinical staff (as part of TAU) work with clients to anticipate and identify internal and external events that may trigger alcohol/drug use or negative affective states. The research staff will further work with the clients to strategically implement the use of the apps for 5 min during or in anticipation of triggers. To promote app usage in both groups, participants will be told that they can earn money towards a gift card that can be redeemed weekly by using the apps at least once per day. If a day passes without their experience of a trigger or ability to use the app, they will be asked to practice the breathing app for 5 min prior to going to bed. From Treatment Week 4 through 12, the research clinicians will continue to collect weekly psychosocial data related to drug/alcohol cravings, mood, triggers, usefulness of the app, timeline follow back, and app usage information. At these assessments, electronic data regarding number of times the app was used, will be downloaded from the participants' iPhones. Three additional VAS will assess strategic app use in the previous week (assessment of triggers over the past week, and usefulness for avoiding alcohol/drug use).

Troubleshooting: During weekly assessments, clinical research staff check in with participants about using the app/ iPhones; 5-10 min booster sessions are provided to ensure that resonance breathing is being performed correctly (i.e., no hyperventilation). A free text messaging app is downloaded onto all phones to allow free texting to the research staff for any questions whenever a wireless signal is available. A research phone is also monitored for questions.

Optional fMRI: If interested an eligible, participants will be invited to complete a neuroimaging scan during the intervention phase. At the scanning facility, participants will provide informed consent and an MRI safety screener. Basic measurements will be collected prior to the fMRI scan. The fMRI scan will last approximately 45 minutes in duration.

Follow-up Phase. During Treatment Week 12, participants will return for lab session 2. Participants will meet with clinical research staff 1 month and 3 months after the completion of the second laboratory visit. They will be asked to complete battery of surveys containing VAS assessments and a psychosocial survey similar to the Addiction Severity Index (ASI) that measures quality of life indexes such as medical problems, psychological problems, drug/alcohol problems, financial problems, social problems, and legal problems.

B. Data Collection

Paced Breathing Application:

CameraHRV, a paced breathing app, is preloaded onto the iPhone participants are given. The app is preset to either the control (14 breaths per minute) or intervention (6 breaths per minute) based on group assignment. Participants are

instructed to use the app at least 5 min/ day, every day for the duration of the intervention. Data from CameraHRV is downloaded during weekly meetings and the second laboratory visit. Data collected from the app include:

- ***Frequency of Use*** – number of days, times, and 5-minute app use sessions.
- ***Physiology*** –heart rate (HR) and R-spike to R-spike intervals (RRI) from the photoplethysmography during each app use session.

Psychophysiology Data:

- ***Laboratory Sessions****:* Research staff measure height, weight, arm length, and blood pressure. ECG data is collected via electrodes placed on the upper right arm (negative), lower left leg (positive), and upper left arm (ground). Respiration data is collected using an abdominal and thoracic breath belt. Beat-to-beat blood pressure is measured using a finger cuff. Physiology is measured using a PowerLab 16/30 acquisition system (ADInstruments, Colorado Springs, CO) and Finometer MIDI (Finapres Medical Systems, The Netherlands) while participants complete three tasks: a 5-minute baseline vanilla task, a 5-minute paced breathing task at 14 breaths per minute, and a 5-minute paced breathing task at 6 breaths per minute (resonance breathing). For the Vanilla Task, participants are presented with a different color rectangle every ten seconds (rate of 0.1Hz) and asked to silently count the number of blue rectangles. The first paced breathing task will use a visual pacer to help the participant breath at a rate similar to a normal breathing rate (14 breaths-per-minute). The second paced breathing task requires participants to breath at a frequency of 0.1Hz (6 breaths per minute) using a visual pacer. All data will be analyzed using standard procedures (Cooke et al., 1999; Task Force, 1996), and all HRV indices will be calculated using Fourier transformations in WinCPRS (Absolute Alien Oy, Finland), psychophysiology data analytic software and undergo natural log transformations to satisfy parametric assumptions.

- ***Training Sessions***: During the first four of weekly training sessions, participants practice the paced breathing using Thought Technology acquisition software (Thought Technology Ltd., Montreal West, QC). ECG data is collected via electrodes placed on the upper arms, pulse will be collected via a finger cuff, and respiration will be collected using an abdominal breath belt. During the first 3 weeks, participants also breathe at their randomly assigned breathing rate with the aid of a visual pacer while being able to see their physiology signals on the computer screen. During the final practice week, the session is recorded.

- ***fMRI Physiology*****:** If eligible, participants are invited to complete two fMRI sessions at the beginning (week 3) and end (week 12) of the intervention. During these sessions, basic physiology measurements are collected outside of the fMRI scanner such as height, weight, arm length, and blood pressure. Participants will be asked to report the first day of their last period and required to demonstrate a negative pregnancy test (via urine dipstick) prior to entering the scanner. While in the fMRI physiology data will be collected via Biopac Software (Biopac Systems, Goleta, CA) and Caretaker software. ECG data will be collected via electrodes placed on the chest, beat-to-beat blood pressure will be collected via a finger cuff, and respiration will be collected using an abdominal belt.

*Clinical Interviews (*administered by trained clinical research staff):

- ***Structured Clinical Interview for DSM-V (SCID-5)*** – A semistructured interview for making substance use disorder diagnoses (First et al, 2016). It is administered prior to the intervention.
- ***Mini-International Neuropsychiatric Interview (MINI)*** – A brief structured diagnostic interview to assess the 17 most common psychiatric disorders in DSM-5. It is administered prior to the intervention.
- ***Important People Assessment (IPA)*** – A clinical interview of social network and activities, including support from family and friends for sobriety and continued drinking. It is administered prior to the intervention and at the end of the intervention.

Self-Report Measures:

- ***Health and Demographic Questionnaire*** –Participants will be asked a variety of questions regarding health and demographic information such as age, race/ethnicity, marital status, education information.
- ***Medical Condition Checklist***- is a self-report questionnaire that asks study participants to identify medical conditions and medications taken at the time of the lab visits.
- ***Addiction Severity Index*** **(ASI)** - A semi-structured interview about medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status (past 30 day and lifetime). The ASI is collected by the participant's addiction treatment provider prior to entering the research study. Participants give their consent and sign a release of information to allow this survey to be shared with research staff.

- ***Penn Alcohol Craving Scale (PACS)*** – A five-item self-administered instrument for assessing craving. Frequency, intensity, and duration of thoughts about drinking/substance use are assessed along with ability to resist drinking/substance use. The final item asks the responder to provide an average rating of his/her craving over the course of the past week. The questions on the PACS use descriptors coupled with numerical ratings ranging from 0 to 6. The PACS will be administered weekly (Flannery et al.,1999)
- ***Inventory of Drug Taking Situations (IDTS)*** – A 50-item questionnaire about situations in which a client has used alcohol or another drug over the past year. Frequency of heavy drinking or drug use in each of 50 situations on a 4-point scale ranging from "never" to "almost always." Eight subscales are computed: unpleasant emotions, physical discomfort, pleasant emotions, testing personal control, urges and temptations, conflict with others, social pressure to use, and pleasant times with others. The IDTS is administered pre and post intervention. (Annis and Martin, 1985),
- ***Post-Traumatic-Stress-Disorder Check List for DSM V (PCL-5)*** – The PTSD Checklist for DSM-5 is a 20-item self-report measure that assesses the presence and severity of PTSD symptoms. Items on the PCL-5 correspond with DSM-5 criteria for PTSD. (Blevins et al., 2015).
- ***Beck Anxiety Inventory (BAI)*** **and** ***Beck Depression Inventory (BDI-II*****)** – Both are 21-item multiple-choice self-report inventory that measures the severity of anxiety and depression symptoms, respectively. Both are administered pre and post intervention. (Beck et al, 1988, 1996)
- ***Emotional Regulation Questionnaire (ERQ)*** – A 10-item scale designed to measure tendency to regulate emotions via: (1) Cognitive Reappraisal and (2) Expressive Suppression. Each item uses a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). The ERQ is administered pre and post intervention.
- ***UPPS-P*** – A 59-item self-report measure of trait/personality-type impulse behavior across 5 subscales (urgency, premeditation, perseverance, sensation seeking, and positive urgency) based on acts/incidents over the past 6 months and rated on a 4-point scale(1-Agree strongly to 4-Disagree strongly). (Whiteside and Lydam, 2001)
- ***Positive and Negative Affect Scale (PANAS)*** - A 20-item test of positive and negative affect using 5-point scale that ranges from very slightly or not at all (1) to extremely (5) (Watson, Clark, Tellegan 1988) The PANAS is administered weekly for the duration of the intervention.
- ***Visual Analytical Scales (VAS)*** – are administered weekly during the intervention and at the follow ups to assess exposure to drug-using triggers (negative situations, positive situations, and temptation situations) on a scale 1 to 100 as well as usefulness of the app over the past week.
- ***Follow Up Surveys*** – assess how bothered by problems in different areas of life addressed in the ASI at 1 month and 3 months post-intervention.

Active Substance Use:

- ***Timeline Follow Back (TLFB)*** – A retrospective assessment method to track daily substance use using a calendar to enhance recall (e.g., calendar; key dates serve as anchors for reporting substance use; standard drink conversion). It is administered prior to the intervention (90 day recall period) and weekly throughout the intervention, and at the follow up assessment. (Sobell et al, 1996)
- ***Urine Drug Screen data*** – Random urine drug screens are collected throughout the research study by the addiction treatment site as part of treatment as usual. Participants consent to share their drug screen results and will sign a release of information to share the data with trained research staff.

*Cognitive Data (*collected both before and after the intervention)*:*

- ***Trails-A and Trails-B*** and ***Symbol Digit Modalities Task (SDMT),*** two well-validated and highly reliable measures of different domains of executive function are administered using the c3 application (NeuroLogix Technologies, Cleveland, Ohio) on a lab-based iPad.
- ***Stroop Test*** (all 3 pages), an additional well-validated and highly reliable measure of executive function is administered using a paper and pencil method.

fMRI Data:

Neuroimaging data is collected pre and post intervention using a 3T Siemens Trio scanner and a Siemens 12-channel head coil. A T_1-weighted MPRAGE protocol will be used to obtain high-resolution anatomical images. Participants who are eligible and willing to participant in the fMRI portion of the study will complete 5 tasks while in the scanner: two resting tasks at the beginning and end of the scan, a baseline vanilla task, the two breathing tasks (14 breaths per minute, and 6 breaths per minute) practiced at the laboratory visit, and the Flanker cognitive task.

- ***Flanker Task*** –participants are shown a series of either congruent or incongruent arrows flashing on the screen, using a two button response box, participants are instructed to select the direction of the middle facing arrow. The Flanker task is scored based on the number of correct responses.

C. Process of Data Collection:

The consenting process, clinical interviews, pre-intervention surveys, and weekly meetings take place while the participant is in treatment at usual (TAU) at the Center of Great Expectations. Two laboratory sessions (pre- and post-intervention) are conducted at the Cardiac Neuroscience Laboratory by trained research staff. Participants will be assigned an ID number when consented into the study. This ID will be on all surveys.

Consent (~1 hour): A trained clinical research staff recruit participants directly from treatment during approximately the clients 2nd week of treatment. The informed consent is explained to and signed by the participant. Participants also sign a release of information to get additional information from CGE, complete a contact form, and complete the Health and Demographic Questionnaire.

Pre-Intervention Phase: Clinical research staff conduct clinical interviews to verify substance use disorder and mental health disorder diagnoses, and understand the participant's social circle. Participants complete a battery of self-report questionnaires regarding triggers for substance use, cravings for drugs/alcohol, and screen for post-traumatic stress disorder. Participants complete a 3-Month Timeline Follow back assessment to track drug use 3 months prior to entering the study. Once these surveys are complete, the lab visit and first fMRI appointment (if eligible) are scheduled.

Lab Visits: Basic measurements (height, weight, arm length) are collected and cognitive tests (Stroop, Trails A and B, and SDMT) are completed. ECG, respiration, and beat-to-beat blood pressure are recorded during 3 tasks: baseline vanilla task, paced breathing task at 14 breaths per minute, and paced breathing task at 6 breaths per minute (resonance breathing), in that order. participants are then given lunch and instructed to fill out a battery of self-report surveys and complete a Timeline Follow Back assessment. During the first lab visit, clinical research staff will instruct participants on types of triggers, and train the participant on how to use the iPhone breathing app.

Intervention Phase: Participants meet with clinical research staff for ~15-20 minutes while they are present at the treatment facility. During the first 4 weeks of treatment, Thought Technology software, with electrodes on upper arms, a respiration belt around the waist, and a finger cuff on the middle finger to measure pulse) is used to visualize physiological response to breathing interventions. Participants practice the paced breathing exercise. Clinical research staff ensure correct breathing techniques. At the fourth session, the breathing session is recorded. Clinical research staff check the participant's study phone and download data from the paced breathing app. Participants then complete a battery of self-report surveys, and a weekly Timeline Follow-Back. Incentives for app use and bringing the phone with them to the session are then provided.

Neuroimaging data are collected pre and post intervention using a 3T Siemens Trio scanner and a Siemens 12-channel head coil located at Rutgers Brain Imaging Center (RUBIC), Rutgers: Newark. Consent is reviewed and the imaging arrival protocol is completed. Imaging is performed using a Siemens TRIO 3T magnet. Participants view visual cues by looking in a mirror attached to the head coil. T1-weighted axial anatomical scans (TR=1900ms, TE=2.52ms, FOV=256mm, slice thickness 1mm, 0.5mm gap, 176 slices) is obtained prior to the experimental trial sequence for registration with functional data and visualization purposes. Echo planar gradient echo imaging sequence and axial orientation will be used for collection of the functional data (TR=2000ms, TE=25ms, matrix size=64x64, FOV=192mm, slice thickness 3mm, 1mm gap, 35 slices). To minimize echo planner imaging (EPI) distortions and facilitate acquisition, a field map is acquired (TR=430ms, TE=7.35/9.81ms, FOV= 192mm, 40 4mm slices, no gap); total imaging time =1min 46s. Thus, two gradient echo images that differ in TE by 2.46 ms are acquired. Gradient echo imaging is used due to better signal-to-noise ratio. ECG and respiration are collected using a MRI-compatible BIOPAC acquisition system (Biopac Systems, Goleta, CA). Beat-to-beat BP is assessed with a MRI-compatible NIBP-MRI CareTaker system (Biopac Systems, Goleta, CA). Cardiovascular recording are synchronized with fMRI scanning at the beginning of the first task. Participants first complete a resting state task followed by the vanilla task, 2 paced breathing tasks using the visual pacer, a cognitive task and a second resting state task. There are a 30-sec inter-task interval. Total scan time is approximately 45 min.

D. Study Duration

Participants complete two pre-intervention meetings with research staff during treatment as usual to complete the consenting process, self-report questionnaires, and the clinical interviews and will take approximately 2 hours each. The iPhone app intervention is an 8-week study with 2 follow-up interviews. There are two 3-hour lab sessions at the Cardiac Neuroscience Laboratory, on Busch Campus of Rutgers – New Brunswick (less than 10 minutes from CGE). Transportation

will be provided for participants so that they can easily make their way to the lab without getting lost on campus. During the intervention, participants meet with study staff once a week for 15-20 minutes Follow-up assessments take approximately 15-20 minutes. A subset of participants are invited to complete two neuroimaging sessions (~2.5 hours each) at the Rutgers University Brain Imaging Center (RUBIC) in Newark, NJ. Transportation is provided. The the study will span ~5 months.

Timetable/Schedule

- ➔ Recruitment / Pre-Intervention Phase
  - Week 0: Consent
  - Week 1: Pre-Intervention Phase week 1
  - Week 2: Pre-Intervention week 2
  - Week 3: Lab Visit 1 / fMRI 1 (if eligible)
- ➔ Intervention Phase
  - Week 4 -11: Weekly meetings at CGE
  - Week 12: Lab Visit 2 / fMRI 2 (if eligible)
- ➔ Follow-Up Phase
  - 1 Month Follow-Up
  - 3 Month Follow-Up

E. Primary Study Variables

The independent variables are frequency of iPhone app use (number of days the app was used, number of times the app was used, and number of times the app was used for the prescribed five minutes). The dependent variables are changes in alcohol and drug use, anxiety, craving, and depression from during and after treatment; physiological changes (HRV) pre- to post- intervention, and, for a subset who participated in the fMRI study, changes in BOLD signal.

Human Subject Considerations

Method to Identify Potential Subjects

Women who are receiving treatment for alcohol and other drug use disorders at the Center for Great Expectation (CGE) are eligible for the study. CGE specializes in helping women through pregnancy, early parenting, and addiction recovery by providing treatment for addiction and co-occurring conditions.

Recruitment Details

Recruitment takes place at CGE during week 2 of the treatment program. The Rutgers research staff coordinate with clinical staff to recruit participants following group therapy sessions. All non-pregnant women are invited to participate, and all are explicitly told their non-participation in no way affects the treatment they receive from CGE.

Inclusion Criteria

All women who are receiving outpatient treatment for alcohol and other drug use disorders at CGE.

Exclusion Criteria

Pregnant women are excluded due to the hormonal implications on cardiovascular functioning and the inability to recruit sufficient numbers of pregnant women to statistically analyze or model separately. MRI contraindications are exclusionary for a subset of women asked to participate in the neuroimaging sessions.

Total Number of Subjects

The proposed study seeks to enroll 175 women with an attrition rate of approximately 20%.

Consent Process

The consenting process takes place at the Center for Great Expectations. Participants are informed that they can withdraw from the study at any time without interfering with their treatment at CGE. Participants are reminded prior to filling out each survey battery that they do not need to fill out any questions they do not feel comfortable answering. The consenting process takes ~1 hour, an additional ~20 min for consenting into the fMRI portion of the study. When reviewing the consent form and outline of the study with the participants, participants are given a chance to ask questions and ask for clarification after every section of the consent form. Participants are given study outline handouts that clearly lay out each portion of the study, where it takes place, how long it takes, and what they will be compensated. Participants are given time to read and review the consent form and then given time to ask any additional questions. Once it is clear the participant understands the study and consent process, they are asked to sign the consent form.

Expenses and Compensations
There are no expenses for participants to take part in the research study. Participants receive compensation throughout the study as follows:

- iPhone App Use Compensation: Participants will receive $1 towards a Dunkin Donut gift card each time they use the app (max: $10 per week). Participants who use the app at least 21 days out of the month receive a $10 bonus (up to 2 monthly bonuses)
- Remembering the iPhone for App Data Download: We use a Contingency Management approach to incentivize participants to bring their study phones with them to treatment. They can win a prize each time they bring their phone from drawing a slip of paper from a jar (numbered 1, 2, or 3, corresponding to value of prizes - $1 to $5).
- Study Completion: Participants who complete the second laboratory visit receive a $50 Walmart gift cards and can keep the iPhone that they used during the study. Participants who already own an iPhone 5s or newer will have the option of trading in the study iPhone for the value of the study phone in Walmart gift cards.
- Follow-Up Surveys: Participants receive $25 in Walmart gift cards for completing the follow-up surveys.
- fMRI Sessions: Participants who complete the fMRI sessions will earn $50 in Walmart gift cards per fMRI session. There are two fMRI session (one pre and one post intervention), therefore participants can earn a total of $100 in Walmart gift cards for completing both fMRI sessions.
- Lunch: Since most laboratory sessions and fMRI sessions take place following treatment, participants are provided with lunch (up to $10) for both laboratory sessions, and both fMRI sessions.

Description of Risks of Harm to Subjects
Risks to subjects include breaches of confidentiality of sensitive information, distress due to completion of questionnaires and interview requesting sensitive information, and possible short term hyperventilation during slow breathing. The iPhone or iPhone app may be frustrating to learn for some participants.

Minimizing Risks of Harm
Participants are trained in using the iPhone app and instructed to contact research staff with any questions or concerns during the study period. They receive ongoing training related to the breathing techniques used by the app and in the lab to avoid hyperventilation. If the participant endorses suicidality, thoughts of self-harm, or thoughts of harming others, the participant's counselor at CGE will be notified. Although our data are not valid for clinical diagnosis, if we detect a possibly abnormal ECG during our laboratory sessions, we will inform the participant and, if they wish, their clinician at CGE will be notified in the event that the participant might want to follow up with a physician.

We assign unique identifiers to each participant and use these numbers on all paper and electronic data records. The list linking the numeric identifiers to participants' names is maintained in a locked filing cabinet in a locked office. Electronic data files are stored on password protected computers. All permanent copies of electronic date files areidentified by ID numbers only and stored on a fire-walled and password protected server that is dedicated to our research laboratory and maintained by Rutgers OIT-NBCS System site by contract. A copy of imaging data is also stored on a secure server maintained by RUBIC during the course of the study. The linking list will be destroyed within 5 years of study completion.

Only select members of the clinical research staff meet with study participants and gather personal information (contact information) about the research. All other research staff receive limited information on the research participant such as first name only and ID number. If a participant expressed discomfort in working with certain research staff, accommodations will be made to limit contact.

Potential Benefits to Subjects
We hypothesize that using a paced breathing app will benefit participants in terms of decreased alcohol and drug craving, and decreased anxiety and depression symptoms. In addition, this research will benefit society by potentially developing innovative and accessible tools for alcohol and drug problem intervention and treatment.

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