Protocol: Glial Regulators for Testing Comorbid Posttraumatic Stress Disorder and Substance Use Disorders
NCT:02911285
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Hypotheses

Hypothesis 1: Participants receiving N-acetylcysteine (NAC), as compared to placebo, will demonstrate significantly greater reduction in SUD severity and craving from baseline to end of treatment (week 8).

Hypothesis 2: Participants receiving N-acetylcysteine (NAC), as compared to placebo, will demonstrate significantly greater reduction in PTSD severity from baseline to end of treatment (week 8).

Hypothesis 3: Prefrontal cortex-amygdala connectivity at rest and in response to cues will predict reduction in SUD and PTSD severity.

METHODS

Overview: A randomized, double-blind, placebo-controlled clinical trial among individuals (N=90) with SUD and PTSD will be conducted to test the hypothesis that N-acetylcysteine (NAC) will significantly reduce SUD severity, craving, and PTSD symptoms. A subset of enrolled subjects between the ages of 21-40 will complete neuroimaging procedures before and after treatment. All procedures will be reviewed by the MUSC IRB and the Ralph H. Johnson VA Research and Development committee prior to study start.

Participants: Ninety male and female participants between the ages of 18 to 75 with current AUD/SUD and comorbid PTSD or sub-threshold PTSD will be recruited to participate in the study.

Recruitment: Primary recruitment sites include (1) the Ralph H. Johnson VAMC outpatient Substance Treatment and Recovery Clinic (STAR) and (2) the PTSD Clinical Team (PCT).

Inclusion/Exclusion Criteria: To be included, subjects must (1) be 18-75 years old, (2) meet DSM-5 criteria for current PTSD or subthreshold PTSD, and (3) meet DSM-5 criteria for current AUD/SUD. Exclusion criteria include: (1) schizophrenia, bipolar disorder or an eating disorder; (2) any significant medical illness (e.g., asthma) that may adversely affect safety or study participation; (3) psychotropic medication initiation within 4 weeks of study participation or use of the following medications: carbamazepine, phenytoin, nitrous oxide, methotrexate, 6-azauridine triacetate, nitroglycerin or any other medication that may have an adverse interaction with NAC; (4) pregnant or nursing women; and (5) clinically significant suicidal ideation and intent.

General Procedures: Interested individuals will be screened for eligibility. Individuals who meet inclusion/exclusion criteria will be invited to come into the office for a comprehensive baseline assessment. Potential participants will be given a full description of the study and asked to read and sign an IRB-approved informed consent form before any study procedures or assessments are conducted. Baseline assessment will include diagnostic interviews, history and physical examination, assessment of concomitant medications, self-report questionnaires, breathalyzer and urine drug screen (UDS), and pregnancy test for females. Ineligible participants will be referred clinically for treatment. Immediately following the baseline visit, eligible participants between the ages of 21-40 will complete a neuroimaging session (described in the Neuroimaging Component section) prior to medication initiation. This same subset of participants will complete a second neuroimaging scan during week 8 prior to medication discontinuation. All participants will enter an 8-week, randomized, double-blind, placebo-controlled trial in which they will be seen once weekly.

Study Medication, Dosage, and Administration: The starting and continuation dose of NAC will be 1200mg bid (2400mg/day). Medication will be dispensed weekly and participants will be asked to return the prior week's medication container in order to account for unused medication and to assess medication compliance. Equivalent number of matching placebo capsules will be dispensed. Study medications (USP-grade NAC and matched placebo capsules) will be packaged by Pitt Street Pharmacy in Mount Pleasant, SC and dispensed to participants by the medical clinician. All NAC and placebo capsules will also contain riboflavin 25 mg, which will be used as a biomarker for medication compliance. Participants who wish to take a multivitamin during the treatment phase of the study will be given a multivitamin that does not contain riboflavin. Treatment assignment will follow a pre-

arranged randomization scheme and be carried out by a pharmacist not involved in clinical management of participants (to preserve the double-blind design). Subjects will be maintained at the target dose for 8 weeks. Side effects and adverse events will be evaluated weekly.

Cognitive Behavioral Intervention: Participants will receive 1-hour each week of manual-based, cognitive behavioral therapy (CBT) for AUD/SUD. Receipt of weekly CBT during the treatment phase will facilitate retention and medication adherence, ensure that all participants receive adequate psychosocial support regardless of medication arm, and enhance statistical power (Carroll et al., 2004). Sessions from the Cognitive Behavioral Coping Skills Manual (Kadden et al., 2003) will be used, for example: Coping with Cravings and Urges to Use, Managing Thoughts about Alcohol/Drug Use, Problem Solving, Alcohol/Drug Refusal Skills, Planning for Emergencies and Coping with a Lapse, and Managing Negative Moods and Depression. All Study Therapists will complete a formal training of the intervention. To help maintain treatment integrity, we will use a manualized treatment, provide intensive bi-weekly supervision to reinforce and sustain clinicians' skills in therapy delivery, and monitor fidelity to the treatment manual using methods developed in the NIMH Collaborative Study to prevent therapist "drift" (DeRubeis et al., 1982).

Assessment Instruments: After the informed consent procedure, subjects will complete a battery of assessments. The instruments to be used were selected because many are standardized, have good psychometric properties, are widely used and have been used by our research group. The primary clinical outcomes include: alcohol/substance use severity (TLFB), craving (OCDS), and PTSD symptom severity (CAPS-5).

General Diagnostic and Inclusion/Exclusion Criteria

- Demographics and Military Service Characteristics Form: This form measures demographics (e.g., age, race, gender, education, marital status) and military service information, such as branch and rank.
- Treatment Services Review: This form obtains information about the participant's ongoing/new treatment for alcohol/substance use and PTSD.
- Mini International Neuropsychiatric Interview 7.0 (MINI 7.0; Sheehan et al., 1998): The MINI will be used to diagnose AUD, SUD, and confirm other exclusionary psychiatric diagnoses.
- History of Head Injuries: A questionnaire that will be administered at Baseline, and Week 8 for anyone participating in fMRI, to assess for head injuries.

Vital Signs, Adverse Events and Medication Compliance

- Vital Signs: Orthostatic blood pressure, pulse measurements, weight and body mass index (BMI) calculations will be measured at baseline, Week 4, and Week 8.
- Adverse Events (AEs): AEs will be assessed at baseline, weekly during treatment, and at follow-up. The type of AE, severity of the AE, duration of the AE, and relationship of AE to study medication will be recorded.
- Concomitant Medications: All concomitant medications will be recorded on a standard form throughout the study. Multivitamins supplied by the study will be recorded and inquiries will be made about daily compliance.
- Medication Accountability Log: This is a document describing a one-week schedule recording days of study medicine taken. Returned medication packages will have capsules counted and recorded.
- Riboflavin Test: All medication capsules, NAC and placebo, will contain 25mg of riboflavin. A urine assay will be collected at medication initiation (at baseline for telehealth participants), week 4 and week 8 to test for medication compliance.

Table 1. Assessment Instruments and Timeline

Instrument	Baseline	Medication Initiation	Medication and Symptom Monitoring								Follow Up
Weeks →	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1 & 3 Mth**
Demographic Data	X										
History and Physical Examination	X										
MINI Diagnostic Interviews	X										
Concurrent Medications Form	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X					X				X	
Medication Log		X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test for Females	X					X				X	
Urine Drug Screen: UDS	X					X				X	X
Riboflavin Test		X				X				X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Breathalyzer/Saliva BAC Tests	X	X	X	X	X	X	X	X	X	X	X
Timeline Follow- Back: TLFB	X	X	X	X	X	X	X	X	X	X	X
CIWA-AR	X										
Visual Analog Scales; VAS	X	X	X	X	X	X	X	X	X	X	X
Obsessive Compulsive Drinking Scale: OCDS	X	X	X	X	X	X	X	X	X	X	X
Ethyl glucuronide (EtG)		X				X				X	X
Clinician Administered PTSD Scale: CAPS-5	X					X				X	X
PTSD Checklist: PCL-5	X		X	X	X	X	X	X	X	X	X
Life Events Checklist: LEC-5	X										
Childhood Trauma Questionnaire: CTQ-SF	X										
Beck Depression Inventory-II: BDI-II	X		X	X	X	X	X	X	X	X	X
Deployment Risk & Resiliency Inventory-2	X										
Columbia Suicide Severity Rating Scale	X					X				X	X
Penetration of the Blind Questionnaire										X	
AUDIT	X										
Cognitive Testing		X				X				X	
Blame Questionnaire	X									X	
Fagerstrom	X										
Coping Inventory	X									X	
Visual Analog Scale: VAS - fMRI	X									X	
History of Head Injuries BL	X										
History of Head Injuries FU										X	
Satisfaction Questionnaire										X	X
Treatment Services Review	X	X	X	X	X	X	X	X	X	X	X
Neuroimaging Procedures	■									■	
Cognitive Behavioral Therapy: CBT			♦	♦	♦	♦	♦	♦	♦	♦	

Alcohol/Substance Use Disorder and Craving

- Timeline Follow-Back (TLFB; Sobell & Sobell, 1992): The TLFB obtains retrospective self-report of substance use by using a calendar and memory prompts to stimulate recall. Quantity and frequency assessments are made using this instrument (e.g., total number of standard drink units, percent of days using) as well as abstinence (yes/no). TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports. The TLFB will assess consumption of alcohol (standard drink units) for 60 days prior to study entry, during the treatment and follow-up phase. Use of nicotine and other drugs of abuse, including prescription drugs, will also be assessed using the TLFB.

- Alcohol Breathalyzer Test will be used to measure blood alcohol concentration (BAC) on a weekly basis for in person visits. Samples reading >0.01 g/dl will be considered positive.
- Alcohol Saliva Test will be used to measure blood alcohol concentration (BAC) on a weekly basis for telehealth visits. In front of the camera, participants will open the one time use test strip, place strip on tongue for 10 seconds, then hold test strip and a color chart to the camera for a study team member to assess. Samples reading >0.01 g/dl will be considered positive.
- Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995): The OCDS is a 14-item self-report measure of craving with high internal consistency and concurrent validity, and good predictive validity of future drinking (Anton et al., 1995; Drobes & Thomas, 1999). It will be used to assess craving.
- Visual Analog Craving Scale (VAS): A Modification of the Within Session Rating Scale (Childress et al., 1986) will be used to assess subjective ratings including craving (amount, frequency), stress and mood, with anchors from 0 = “none” to 10 = “extreme”.
- Visual Analog Scale (VAS) fMRI: A modification of the Within Session Rating Scale (Childress et al., 1986) will be used to assess subjective ratings including craving and stress before and after the fMRI scan.
- Clinical Institute Withdrawal Assessment of Alcohol-Revised (CIWA-Ar; Sullivan et al., 1989): The CIWA-Ar is a widely used, 10-item clinician administered instrument that will be used to assess alcohol withdrawal symptoms. Subjects experiencing significant withdrawal, as evidence by a score of $\geq$ 10, will be assessed by the Study Physician (Dr. Hamner) and referred clinically for medically supervised detoxification.
- Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001): The AUDIT is a 10-item self-report screening measure, developed by the World Health Organization (WHO), with three subscales (alcohol consumption, drinking behavior, and alcohol-related problems). Items are summed for a total score of 40. The AUDIT has good internal consistency (αs = .80-.93) as well as sensitivity and specificity.
- Urine Drug Screen (UDS) tests: Urine samples will be tested with a Multi-Drug Panel Test, which allows for the detection of THC/Marijuana, Cocaine, Phencyclidine, Opioids, Methamphetamines, Amphetamines, Barbiturates, and Benzodiazepines.
- Ethyl glucuronide (EtG): The conjugated alcohol metabolite EtG remains positive in urine for several days following cessation and is a useful biomarker of drinking in outpatient settings (Litten et al., 2010). This will be used as a biologic assessment of drinking, as breathalyzer tests only assess very recent alcohol use. The assay will be done at MUSC on samples collected at medication initiation, week 4, week 8 (end of treatment), and the follow ups.
- Fagerstrom Test for Nicotine Dependence (FTND): Assesses the intensity of physical addiction to nicotine related to cigarette smoking. There are six questions that provide a total score range of 0-10, higher scores indicate a higher physical dependence (Heatherton, et al., 1991). It will be administered at baseline.

Trauma History and PTSD

- Clinician Administered PTSD Scale (CAPS; Weathers, Keane, & Davidson, 2001): The CAPS for DSM-5 is a 30-item structured diagnostic interview and gold standard for assessing PTSD (Weathers et al., 2014). The CAPS has excellent psychometric properties and diagnostic efficiency (Weathers et al., 2001). The CAPS-5 was revised to accommodate changes made in DSM-5, reduce administration time, and facilitate scoring procedures.
- PTSD Checklist (PCL-5; Weathers et al., 2013): The PCL-5 is a 20-item self-report measure. The PCL-5 is similar in form to the PTSD Checklist (PCL) based on the DSM-5 (Weathers et al., 1993), which has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity (McDonald & Calhoun, 2010).
- Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013): The LEC-5 assesses lifetime exposure to trauma. It includes the list of 16 different events from the original LEC. In addition, two items screen for military sexual trauma. The primary addition to the LEC-5 is a category involving occupational exposure (e.g., paramedic, police, or other first responder).
- Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003): The CTQ is a 28-item self-administered inventory that assesses childhood abuse and neglect. The CTQ-SF contains subscales including physical, sexual, and emotional abuse, and physical and emotional neglect.

- Coping Inventory for Stressful Situations: Situation Specific Coping (CISS: SCC): Assesses an individual's coping preferences for a designated event (Endler & Parker, 1990).

Depression and Suicidality

- Beck Depression Inventory-II (BDI-II; Beck et al., 1996): The 21-item BDI-II is one of the most widely used instruments for measuring the severity of depressive symptoms. Total scores reflect minimal (0-13), mild (14-19), moderate (20-28), or major depressive symptoms (29-63).
- Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2007): The C-SSRS will be used to assess past/lifetime and current suicide ideation. It will be administered at baseline (for study eligibility), week 4 and week 8, and additionally as needed during the trial to monitor subject safety.

Associated Areas of Functioning

- Deployment Risk and Resiliency Inventory-2 (DRRI-2): The DRRI-2 (Vogt et al., 2012) is a suite of 17 individual scales that assess key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health. The following subscales will be used to assess deployment factors: Combat Experiences. We will use the Post-Deployment Life Events and Support scales to evaluate post-deployment factors for Veterans.
- CNS Vital Signs Cognitive Testing: A battery of two tests (Stroop & Shifting Attention) will assess neurocognitive functions.

Compensation: Participants will be compensated $50 for the baseline visit, $50 for each imaging visit, $40 for each completed weekly visit, and $75 for completing each of the follow-up visits. They will be given a $25 bonus if the baseline/first visit is attended as scheduled. Participants who previously consented to the optional neuropeptide Y will receive $15 compensation for completing the second blood draw. Thus, participants may receive up to $755 for completing all visits. Compensation is available in the form of cash, gift card, or check.

Telehealth participants will be offered compensation for travel to and from the three mandatory in-person visits (Baseline, Week 4, & Week 8).

Neuroimaging Component: Given the severe negative outcomes associated with co-occurring AUD/SUD and PTSD and lack of effective treatments, investigation of the neural circuitry and neurochemistry underlying AUD/SUD/PTSD and involved in positive therapeutic response could be important in guiding future treatment development studies. To that end, fMRI and ^{1}H-MRS data will be acquired at baseline and end of treatment on a subset (n=40) of participants to examine (a) glutamate concentrations, (b) resting state connectivity, and (c) response to alcohol/drug, trauma, and neutral cues. Scans will be conducted at the MUSC Center for Biomedical Imaging.

The neuroimaging component will involve three visits, each lasting 60-90 minutes. During visit 1, we will develop the personalized imagery scripts for alcohol/drug, trauma, and neutral cues. During visit 2 (pre-treatment) and visit 3 (end of treatment), we will conduct the fMRI and ^{1}H-MRS scanning procedures. Imagery scripts will be similar to those developed according to standardized procedures (Sinha & Li, 2007) and employed in our ongoing research.

Upon arrival to the imaging facility (Center for Biomedical Imaging), participants will first participate in a mock scanning session to acclimate to the MRI scanner and to practice using the joystick before completing the actual MRI scan. After mock scanning, participants will be screened for metal using a handheld metal detector. Trained staff will position individuals on the scanner bed with foam padding placed around their head to prevent motion. Participants will wear ear buds to listen to the audio-recorded scripts. For co-registration and normalization of functional images, a high resolution T1-weighted MPRAGE anatomical image will be acquired with the following parameters: TR = 2300ms, TE = 2.26ms, flip angle = 8°, field of view = 256mm, slice thickness 1.0mm. The scanning planes will be oriented parallel to the anterior commissure–posterior commissure line. The ACC voxel for ^{1}H-MRS will be placed on midsagittal T1-weighted images, anterior to the genu of the corpus callosum, with the ventral edge of the voxel aligned with the dorsal edge of the genu and a voxel size of 3 x 2.5 x 2.5cm.

Following auto-shimming, single-voxel water-suppressed ^{1}H-MRS spectra will be acquired using a Point Resolved Spectroscopy (PRESS) sequence: Repetition Time (RT) = 2000ms; Echo Time (TE) = 40ms; number of averages = 128; an unsuppressed water spectrum will be co-acquired (TE = 40ms, number of averages = 16), scaled for partial volume effects and relaxation, and used as a concentration reference (Mullins et al., 2008).

Participants will be asked to relax and keep their eyes opened and fixed on a cross-hair for two six-minute runs while resting state data are collected. Following this, participants will be exposed to alcohol/drug, trauma and neutral cues, which will be audio recorded descriptions of the most recent time they used alcohol/drug, details of a traumatic event, and details about a relaxing event.

We will use a block design consisting of a single run in which 4 task blocks alternate with rest blocks. The 4 task blocks consist of a neutral cue followed by a trauma cue followed by a neutral cue then an alcohol/drug cue. To minimize potential carry-over effects, the order of task blocks will be counterbalanced so that half of the subjects in the placebo group and half of the subjects in the NAC group are exposed to the alcohol/drug cue first and the remaining participants in each group are exposed to the trauma cue first. This order will be repeated at the end of treatment scan. T2*-weighted gradient-echo planar images (EPI) will be acquired with the following parameters: TR = 1100ms, TE = 30ms, flip angle = 65º, matrix 64 x 64, field of view = 192mm, slice thickness = 3.0mm, with 48 slices to cover the entire brain.

Statistical Analyses: Baseline clinical and demographic characteristics will be collected and contrasts performed between treatment groups. Baseline characteristics found to be significantly associated with primary outcome measures will be included as covariates in the analyses. In general, less than 10% missing data have little impact on power and do not introduce bias, regardless of the missing data mechanism. If the percent missing data are greater than 10%, propensity score methods will be used for data imputation.

We plan to use REDCap for data capture and management. REDCap (Research Electronic Data Capture) is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data (Harris et al., 2008; Harris et al., 2007). REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel.

Power and Sample Size Estimation. It is expected that subjects treated with NAC, as compared to placebo, will exhibit significantly lower PTSD symptoms and craving at week 8. The effect sizes for these analyses (d = 1.27, d = 1.03, respectively) are based on our PoP data. A sample size of 26 would provide power (1-ß) of .80 to detect a large effect size with a Type 1 error protection level of .05 (Cohen, 1988). It is expected that NAC, as compared to placebo, will exhibit significantly lower AUD/SUD severity at week 8. To date, no published studies have examined NAC for the treatment of AUD. Assuming a medium effect size (d = .2), with a Type 1 error protection level of .05 and (1-ß) = .80, a total sample of 58 would be required. Recent unpublished pilot data conducted by our group examining the effects of NAC vs. placebo on standard number of drinks among patients with cocaine dependence and comorbid AUD (n=28) found a statistically significant treatment group effect. With regard to neuroimaging, a recent study of 29 individuals (PTSD=14, controls=15) observed significant differences in PFC-AMY resting state connectivity (Sripada et al., 2012). The effect size for this difference was 0.8 (Cohen's d). Thus, power (1-ß) reaches .80 with a total sample size of N=26 (two-tailed, α = .05). Another study of 45 cocaine-dependent individuals showed that lower PFC-AMY connectivity at baseline predicted relapse (McHugh et al., 2014). The effect size for this reduction was 1.0. Thus, power (1-ß) reaches .80 with N=34 subjects (two-tailed, α = .05).

Hypotheses: The hypotheses and statistical approaches for testing each hypothesis are listed below.

Hypothesis 1: NAC treatment will result in significantly greater reduction in AUD/SUD severity and craving, as compared to placebo. To test this hypothesis, a mixed effects modeling framework will be specified with the

total number of standard drinks consumed and the OCDS total score as the primary outcomes. A Poisson distribution will be assumed with a logarithm link function to assess the effects of NAC treatment. Data collected in substance abuse studies often contain a preponderance of zeros, and these zeros in the distribution can be considered sampling zeros in the Poisson process (Bandyopadhyay et al., 2011). If this excess is present in the distribution, two-part Hurdle models (Poisson and NB) will be explored (Cragg et al., 1971). The hurdle part of the model will allow us to estimate the probability of abstinence during the study period (as an odds ratio) while the Poisson/NB portion will allow for the assessment of the risk of an increase in using days beyond zero during the study period (as a risk ratio). Baseline alcohol/substance use and craving will be included in pertinent models as covariates. Additional alcohol/substance use outcomes will be assessed: change in percent drinking days, percent heavy drinking days, EtG, and VAS craving levels.

Hypothesis 2: NAC treatment will result in significantly greater reduction in PTSD severity (CAPS-5) as compared to placebo. To test this hypothesis, generalized linear mixed effects regression models with a Gaussian distribution will be developed to assess group differences while adjusting for baseline CAPS-5 scores. Assumptions of residual normality and homoscedasticity will be checked using statistical test and graphical methods (Residual and Q-Q plots, and Shapiro-Wilk tests) and transformation will be done as necessary. Restricted maximum likelihood methods will be used to estimate the fixed effects and variance components. Additional outcomes (e.g., PCL-5, CAPS-5 symptom subscales) will be examined.

Hypothesis 3A: Prefrontal cortex-amygdala connectivity at rest and in response to alcohol/drug vs. neutral cues will predict reduction in alcohol/substance use severity (total standard drinks).

Hypothesis 3B: Prefrontal cortex-amygdala connectivity at rest and in response to trauma vs. neutral cues will predict reduction in PTSD severity (CAPS-5).

For hypotheses 3A and 3B, the following preprocessing and analytical parameters will be used. Preprocessing: Post-acquisition preprocessing and statistical analysis of imaging data will be performed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library). Data will be preprocessed using scripting tools from FEAT. Non-brain signal will be removed using FSL's BET brain extraction. Scans will be corrected for motion using FSL's linear registration and scans will be spatially smoothed. Participants with head motion $\geq$ 0.2 mm will be excluded from the analyses (Power et al., 2012). Motion artifacts will be identified and scrubbed from each subject's data. Scans will be spatially co-registered with a standardized anatomical template (Montreal Neurological Institute) using a 12 parameter affine transformation. Analysis: Functional connectivity will be measured using a psychophysiologic interaction (PPI) seed-based approach (Friston et al., 1997). PPI analysis is used to assess the functional coupling between different brain regions. The PPI is defined as the change in connectivity of one area (i.e., the seed region) to another in relation to the experimental context (e.g., alcohol vs. neutral cues). PPI analyses for resting state, trauma and alcohol/drug cues will be performed separately. Customized sq. wave forms representing the trauma run (1=trauma block and -1=neutral block) and the alcohol/drug cue run (1=alcohol/drug block and -1=neutral block) will be convolved with a double-gamma hemodynamic response function. A mask of the seed region will be made using a 12-mm diameter sphere located in the center of the AMY using the MNI coordinates (x, y, z = ±22, 0, -22). The transformation parameters described above will also be applied to the mask. For each subject, the mean corrected and high pass filtered time series of the BOLD signal in the AMY will be extracted and used in a single subject whole brain PPI analysis. The PPI model will include the task vector, time series of the BOLD signal in the AMY, a term representing the positive task x seed interaction, and a term representing the negative task x seed interaction. The first level analysis will generate contrast images of the parameter estimates for each of the four regressors. Voxels will be thresholded at $Z > 2.3$ using a corrected cluster threshold of $p=0.05$. The contrast images of the parameter estimates of the positive and negative task x seed interactions will be combined for group-level t-tests to identify regions that exhibited altered connectivity with the AMY during the trauma and alcohol/drug cues as compared to neutral cues. All group-level results will be thresholded at $Z > 2.3$ using a corrected cluster threshold of $p=0.05$. Separate linear regression tests will be used to test for associations between PFC-AMY connectivity at baseline and improvement in AUD/SUD and PTSD symptoms during treatment. Changes in total standard drinks will be

regressed against the parameter estimate obtained from the center voxel from each cluster that exhibited a significant task x seed interaction with the AMY at rest and in response to the alcohol/drug cues (Hypothesis 3A). Changes in CAPS-5 total scores will be regressed against the parameter estimate obtained from the center voxel from each cluster that exhibited a significant task x seed interaction with the AMY at rest and in response to the trauma cue (Hypothesis 3B). Further exploratory analyses will examine change in PFC-AMY connectivity from pre- to post-treatment and associations with other alcohol/drug and PTSD outcomes, both within and between medication groups.

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