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Design of a Randomized Controlled Trial Examining the Efficacy of Oxytocin to Enhance Alcohol Behavioral Couple Therapy

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Abstract

Combining pharmacological interventions with evidence-based behavioral interventions may help optimize treatment outcomes for alcohol use disorder (AUD). While several effective behavioral interventions for AUD have been developed, the vast majority target individual patients, despite evidence that behavioral interventions for couples have the ability to outperform individual treatments for AUD. Alcohol Behavioral Couples Therapy (ABCT) is an evidence-based behavioral intervention for couples that has been shown to significantly reduce AUD severity as well as improve relationship functioning. Accumulating evidence suggests that the neuropeptide oxytocin has the ability to reduce alcohol craving and consumption, symptoms of tolerance and withdrawal, and ameliorate neurobiological deficits associated with AUD. Furthermore, oxytocin has demonstrated the ability to increase prosocial behavior and cognition, and restore sensitivity to natural rewards such as interpersonal relationships. No study to date has examined the ability of oxytocin to enhance ABCT. Thus, the primary objective of this Phase II study is to examine the effects of oxytocin versus placebo in combination with ABCT in reducing AUD severity and improving relationship functioning. We also will utilize neuroimaging techniques before and after treatment to investigate the underlying pathophysiology of AUD among couples and identify prognostic indicators of treatment outcome. The findings from this study might provide critical new information to help inform clinical practice and accelerate research on the pharmacological treatment of AUD.

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Keywords

couple therapy; alcohol; substance use disorder; oxytocin; functional magnetic resonance imaging

1. Introduction

1.1. Research Objectives and Hypotheses

Combining pharmacological interventions with evidence-based behavioral treatments may help maximize and sustain AUD treatment outcomes[1–3]. Alcohol Behavioral Couples Therapy (ABCT)[4] is a manual-guided, evidence-based psychotherapy for the treatment of AUD that simultaneously targets relationship functioning, which is an important mechanism in the etiology, course, and treatment of AUD[5–7]. While adaptive relationship functioning facilitates successful treatment engagement and outcomes[7–9], maladaptive relationship functioning interferes with AUD recovery[10–13] and is a precipitant of relapse risk[14,15]. Thus, ABCT employs cognitive behavioral techniques to (1) reduce alcohol consumption, (2) enhance partners' skills to facilitate recovery (e.g., communication, managing cravings), and (3) enhance relationship functioning. Although ABCT is an efficacious treatment, there is room for improvement, as more than half of ABCT patients report hazardous drinking during treatment and a similar proportion fail to achieve abstinence[5,6,16,17].

Oxytocin is a promising candidate to enhance ABCT via neurobiological and behavioral pathways, including its potential to restore sensitivity to natural rewards such as interpersonal relationships[18]. Dysregulation of the corticolimbic circuitry involving the prefrontal cortex (PFC) and amygdala (AMY) (i.e., lack of "top down" control) likely makes it difficult to inhibit or modulate emotions, reward processing, and cognitions such as compulsive craving-related thoughts central to AUD[19–22]. Lower PFC-AMY connectivity is associated with increased drinking, drug use, and early relapse[21,23–25]. Similar to some existing findings, our team recently found that PFC-AMY connectivity is implicated in less adaptive responses to relationship conflict[26,27]. Importantly, oxytocin attenuates AMY reactivity and increases resting state connectivity between corticolimbic brain regions[28–34], which are critical mediators of emotion regulation and other responses to social stress[28–31,35]. Collectively, these finding suggest that oxytocin is a promising candidate to help restore the neurobiological impairments underlying AUD.

While oxytocin's pharmacokinetic mechanisms of action remain unclear, evidence also suggests that GABAergic transmission could underlie both prosocial and alcohol-relevant effects of oxytocin observed in neurobiological and behavioral measurements[36]. Behaviorally, human and animal studies indicate that oxytocin reduces alcohol withdrawal, tolerance, craving and self-administration[37–42]. However, emerging literature emphasizes individual and contextual differences moderate oxytocin's effects on social behavior[43–49]. These nuanced findings may be explained by the social salience hypothesis[50], which proposes that rather than selectively enhancing prosocial behavior, oxytocin might amplify an individual's current social tendencies which, without corrective intervention, may be maladaptive[11,15,51]. ABCT has demonstrated the ability to insulate couples from maladaptive relationship behaviors that are proven antecedents to hazardous drinking and

relapse by cultivating and implementing new adaptive skills that facilitate recovery[52,53]. Notably, treatment gains are greater among couples who begin ABCT with poorer relationship functioning and greater psychiatric comorbidity[5], and within-session gains predict positive ABCT outcomes[52]. Thus, combining oxytocin with a behavioral intervention such as ABCT will ensure that oxytocin has an adaptive platform to enhance the positive gains made within ABCT sessions.

The primary objectives of the current study are to (1) compare the efficacy of ABCT with oxytocin vs. placebo in reducing alcohol consumption, (2) compare the efficacy of ABCT with oxytocin vs. placebo in improving relationship functioning, and (3) use neuroimaging techniques to determine the effects of treatment on corticolimbic connectivity in response to alcohol and relationship conflict cues. We hypothesize that compared to the ABCT + placebo group, the ABCT + oxytocin group will demonstrate significantly greater reduction in alcohol consumption and significantly greater improvement in relationship functioning from baseline to end of treatment. We also hypothesize that functional connectivity between the prefrontal cortex (PFC) and amygdala (AMY) after treatment will be stronger in participants who receive ABCT + oxytocin compared to those who receive ABCT + placebo. Furthermore, we hypothesize that baseline PFC-AMY functional connectivity in response to alcohol vs. neutral cues will predict the magnitude of change in alcohol use, and that baseline PFC-AMY functional connectivity in response to relationship conflict vs. neutral cues will predict amount of change in relationship functioning.

2. Materials and Methods

2.1. Research Design

This is a 12-week, randomized, double-blind, placebo-controlled trial examining the efficacy of combining oxytocin (40 IU) with ABCT in the treatment of AUD. A repeated measures design with two intervention arms will be used: (1) ABCT + oxytocin compared to (2) ABCT + placebo. Participants will complete follow-up visits 3 months and 6 months following completion of the treatment phase (Figure 1). This study also will examine two validated AUD biomarkers and employ observational coding. Participants who meet eligibility criteria also will have the option to complete neuroimaging scans at baseline and at the end of the treatment phase to examine behavioral and functional-anatomic mechanisms of treatment response (Figure 2). The study will last for approximately five years.

2.2. Participants

Participants are 100 couples (total N=200) aged 18–70 years comprised of the identified patient (IP) with current AUD and their romantic relationship partner. ABCT is equipped to treat couples if one or both partners meet diagnostic criteria for AUD. Thus, provided that at least one partner meets current AUD criteria, the couple is eligible to participate. Couples of any gender identity and sexual orientation are welcome to participate. This study will enroll an equal distribution of men and women IPs to account for sex differences in oxytocin response and maximize generalizability of findings. Additional inclusion criteria are: (1) English fluency and intellectual functioning sufficient to provide informed consent and

accurately complete assessments and participate in treatment as assessed by a criterion of ≥ 26 on the Mini-Mental Status Exam [54], (2) more than one hazardous drinking episode (i.e., >7 drinks per week or > 3 drinks per occasion for women, or >14 drinks per week or >4 drinks per occasion for men) in the past 30 days by the IP, (3) married or cohabiting for ≥ 6 months, or in a committed relationship of at least 1-year duration, (4) maintenance of psychotropic medications on a stable dose for at least 4 weeks before study initiation, and 5) concurrent substance use disorders (e.g., marijuana) are acceptable provided that alcohol is the IP's primary substance of choice. The inclusion of participants with other substance use disorders is essential because of the marked frequency of co-occurrence among patients with AUD. Exclusion criteria include: (1) meeting DSM-5 diagnostic criteria for a history of or current psychotic or bipolar affective disorders, (2) current suicidal or homicidal ideation and intent, (3) severe, unilateral intimate partner violence in the past 6 months as defined by the Revised Conflict Tactics Scale [55], (4) pregnancy or breastfeeding for women, (5) participants with clinically significant medical or psychiatric conditions that in the opinion of the investigators may adversely affect safety or study participation will be excluded and referred for treatment. Participants presenting with, (6) significant withdrawal symptoms as evidenced by a score of ≥10 on the revised Clinician Institute Withdrawal Assessment of Alcohol [56]. Additional exclusions for the neuroimaging component of the study include claustrophobia; cardiac pacemaker; metal fragments in eye, skin, or body; heart valve replacement; brain clips; venous umbrella; history of aneurysm surgery; intracranial bypass, renal, or aortic clips; joint replacements; non-removable hearing aid, neurostimulator or insulin pump; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires; or any other metal implants.

2.3. Procedures

This study was reviewed and approved by the Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC). Following phone screening for preliminary eligibility, participants complete a face-to-face informed consent and baseline assessment. In a private room apart from their partner, participants are given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form before any study procedures are conducted. During the baseline visit, participants complete a breathalyzer, urine pregnancy test (for women), ethyl glucuronide (EtG) testing, metal screening, a history and physical exam, urine drug screen, and a battery of standardized self-report and interview measures (see Table 1 for assessment measures and timeline). Ineligible individuals are referred clinically for treatment. Provided full eligibility criteria are met, participants are scheduled for a visit to complete a blood draw for phosphatidyl ethanol (PEth) and a functional magnetic resonance imaging (fMRI) session (described in the Neuroimaging Procedures section) prior to entering the treatment phase of the study.

2.4. Study Interventions

2.4.1 Study Medication, Dosage, and Administration.—

Participants are randomized in a 1:1 manner to the oxytocin or placebo condition. Specifically, all participants and study staff including investigators, research assistants, assessors, clinicians, and supervisors will be blind to drug condition. In order to ensure that the treatment groups are balanced with respect to alcohol consumption (TLFB) and sex of the IP, a stratified

randomization process will be used. Participants receive the same medication at each session, and partners within each couple are randomized to the same drug condition, meaning that both the IP and their partners will be taking their assigned medication (or placebo). A 40 IU dose of intranasal oxytocin or matching placebo (saline) is self-administered 30 minutes prior to the start of each weekly ABCT therapy session. The dose and timing of medication administration is based on past research in our group and others [47,57–60]. A 40 IU dose has demonstrated extensive safety and efficacy, is within the normal dosing range, and one of the most common concentrations utilized in human research [61–63]. The MUSC research pharmacy compounds and dispenses the oxytocin and matching placebo nasal sprays. Research staff instructs participants on the correct method of administration and observes participants' self-administration. Randomization is carried out by a research pharmacist not involved in clinical management of participants in order to preserve the double-blind design.

2.4.2 Psychosocial Intervention: Alcohol Behavioral Couple Therapy (ABCT)

—All participants receive 12 weekly ABCT therapy sessions delivered by trained clinicians consistent with the published manual [4]. The main goal of ABCT is to concurrently reduce AUD symptom severity and improve relationship functioning. Patients receive psychoeducation pertaining to the interconnectedness of AUD and relationship functioning. AUD-focused components of the treatment help patients identify and manage cravings, urges to drink, and thoughts about alcohol use; enhance individual problem solving and decision-making abilities; identify and plan for "high-risk" situations in which vulnerability to relapse is heightened; learn drink refusal skills; and cope with a potential relapse. ABCT also teaches couples to work together to enhance reciprocity and communication skills in the relationship, increase positive rewards of initiating and maintaining drinking reductions and abstinence, and implement ways partners can help minimize and manage alcohol use triggers, assist each other with drink refusal skills, and help prevent relapse.

2.5. Primary Outcome Measures

The primary outcomes are (1) alcohol consumption and (2) relationship functioning. Alcohol consumption (e.g., percent days abstinent, percent heavy drinking days) is measured by the Time Line Follow-Back TLFB; [64] 60 days prior to study entry, weekly during the 12 weeks of treatment, and at follow-up. The TLFB uses a calendar to stimulate recall, yields consistently high test-retest correlations, and correlates well with other self-reports and collateral reports. Relationship functioning will be assessed using the 7-item version of the Dyadic Adjustment Scale DAS-7; [65]. The DAS-7 is a self-report survey based on the original 32-item measure [66]. It is used to assess four domains relationship functioning and has demonstrated strong psychometric properties [65].

2.6. Secondary Outcome Measures

Additional AUD outcomes include alcohol craving PACS; [67] and ethanol metabolites and traditional biomarkers (e.g., ethyl glucuronide [EtG] and Phosphatidylethanol [PEth]) to corroborate participant self-reports of abstinence and alcohol use [68–70]. PEth is among the most specific biomarkers used to detect heavy drinking and monitor abstinence [71–73]. The conjugated alcohol metabolite EtG remains positive in urine for several days following

cessation and is a useful biomarker of recent drinking in outpatient settings [74]. Additionally, treatment satisfaction, working alliance, and functioning in domains related to AUD (e.g., depression, intimate partner violence, emotion regulation) are assessed. In order to explore secondary outcomes such as the effects of treatment on within-session behaviors, we will employ observational coding to assess frequency of positive, negative, and alcohol change talk behaviors using the System for Coding Couple Interaction in Therapy-Alcohol SCCIT-A; [75] in ABCT sessions 1, 6, and 12.

2.7. Neuroimaging Procedures

All neuroimaging scans are conducted at the MUSC Center for Biomedical Imaging, which houses a Siemens 3T Prisma MRI scanner (Siemens Medical, Erlangen, Germany). Neuroimaging sessions (Figure 2) last approximately 60 minutes each and occur at baseline and week 12. At baseline, personalized imagery scripts are be developed for alcohol and neutral cues according to the manualized procedures described by Sinha and Tuit [76]. Participants also will develop a relationship conflict cue consistent with the procedures described by Flanagan and colleagues [77]. During initial scanner tuning, localizing, and structural scanning, participants are shown “relaxing” images (i.e., 20 scenic pictures, each displayed for 30 seconds). For co-registration and normalization of functional images, a high-resolution T1-weighted MPRAGE anatomical image is acquired with the following parameters: TR = 2300 ms, TE = 2.26 ms, flip angle = 8°, field of view = 256 mm, slice thickness 1.0 mm, 192 slices. The scanning planes are oriented parallel to the anterior commissure–posterior commissure line.

A block design consisting of two 12-minute scans is employed: an alcohol cue scan and a relationship conflict cue scan. The alcohol cue scan is divided into four, 2-minute blocks of alcohol cues and neutral cues separated by 30 seconds of rest plus 30 seconds in which to complete response ratings using a modified version of the Visual Analogue Scale VAS; [78]. During the blocks of alcohol cue, participants listen to an audio-recorded script describing in detail their most salient recent use of alcohol. During the blocks of neutral cue, participants listen to an audio-recorded script describing a relaxing, non-stimulating scenario. The relationship conflict block is also divided into four, 2-minute blocks of relationship conflict cues and neutral cues separated by 30 seconds of rest. During the relationship conflict blocks, participants listen to an audio-recorded script of a conflict task completed in the laboratory with their partner. The same excerpt is used for each block and each visit. To minimize potential carry-over effects, the scans are counterbalanced so that half of the participants in each treatment arm (e.g., oxytocin or placebo) are exposed to the alcohol cue first and the remaining participants in each group are exposed to the relationship conflict cue first. This order is preserved from pre- to post-treatment scanning for each participant. T2*-weighted gradient-echo planar images (EPI) are acquired with the following parameters: TR = 1100 ms, TE = 30 ms, flip angle = 65º, matrix 64 × 64, field of view = 192 mm, slice thickness = 3 mm with no gap, multiband factor = 3, with 51 slices to cover the entire brain. A gradient field map with the same spatial resolution and slices as the EPI is collected to correct for geometric distortions cause by magnetic field inhomogeneity.

2.8. Data Analytic Plan

2.8.1 Power Analysis—This study is powered to detect moderate treatment group differences in percent days abstinent (PDA) and percent of days of heavy drinking (PDH), and relationship functioning as measured by the TLFB and DAS-7, respectively at end-of-treatment (weeks 9–12). Assuming 2-sided hypothesis testing and alpha levels of 0.05, we will have 80% power to detect treatment group differences with effect sizes of 0.6 in the presence of 30% attrition (n=70 couples) during the treatment phase. This approach is consistent with treatment group differences in PDA (d=0.59) and PDH improvements (d=0.79) in a prior ABCT trial (n=102)[5], although we recognize that that trial compared individual therapy vs. ABCT (not ABCT ± medication). In that study, PDA increased from 34.98% ± 29.17% to 80.52% ± 27.75% at the end of treatment in the ABCT group, and PDH decreased from 56.83% ± 28.87% to 10.52% ± 22.16% in the ABCT group. Incorporating an arcsine or other appropriate transformation to account for non-normality of these metrics will enable us to discern whether oxytocin enhances end of treatment PDA by an additional absolute 9% or greater (i.e., to 80.5% in the ABCT+ placebo group vs. 89.5% in the ABCT + oxytocin group) and whether oxytocin further decreases PDH by an absolute 6% or greater (i.e., to 10.5% in the in the ABCT+ placebo group vs. 4.5% in the ABCT + oxytocin group). Another prior ABCT trial found that DAS-7 scores (21.1 ± 6.7) remain relatively constant throughout treatment[6]. We will have 80% power to detect treatment group differences of 4 units of improvement in DAS-7 scores.[79]

2.8.1. General—Baseline clinical and descriptive characteristics will be examined and compared between treatment groups using chi-square tests, Fisher's exact tests, t-tests, or Wilcoxon rank sum tests, as appropriate. Baseline characteristics that are significantly different between treatment groups will be included as model covariates, and sex will be included as a primary demographic covariate in order to account for potential sex differences in primary and secondary outcomes. The primary analysis will focus on end-of-treatment (i.e., the final three weeks of the treatment phase) outcomes among IPs using an intent-to-treat framework. Participants who decline to continue in treatment prior to session 12 will be invited to complete all remaining study assessments.

2.8.2. Clinical outcomes—We hypothesize that as compared to the ABCT + placebo group, the ABCT + oxytocin group will demonstrate (1) significantly greater reduction in alcohol consumption from baseline to end of treatment (PDA and PDH measured by TLFB), and (2) significantly greater improvement in relationship functioning (measured by DAS-7) from baseline to end of treatment. To test hypotheses 1 and 2, a generalized linear modeling (GLM) framework will be used with appropriate link functions, treating end-of-treatment (weeks 9–12) percent days abstinent (PDA), percent days hazardous drinking (PDH), and DAS-7 scores as dependent variables (in separate models), and treating treatment group (ABCT + oxytocin vs. ABCT + placebo) as the primary independent variable. Baseline values for PDA, PDH, and DAS-7 will be included as covariates, along with sex and other potentially significant baseline characteristics. Treatment group x sex interactions will be explored, to gain a sense of whether the treatment is more efficacious in men vs. women or vice versa. Since PDA and PDH may exhibit non-Gaussian distributional forms and/or zero-inflation, alternative modeling strategies (e.g., arcsine or Box-Cox transformations, two-part

Hurdle models) may be explored. Model fit will be compared by examination of Likelihood Ratio chi-square values. If transformations are necessary, inverse-transformations will be used in conveying the model results. Generalized estimating equation models will be used in secondary analyses comparing time trends in the outcomes over the course of the study.

2.8.3. Neuroimaging outcomes—Pilot work conducted by our team compared the effects of a novel auditory relationship conflict cue versus a validated neutral cue on functional connectivity in corticolimbic brain regions. We also explored sex differences in neural correlates of relationship conflict. Participants demonstrated greater PFC-AMY functional connectivity during the relationship conflict cue compared to the neutral cue. Women, as compared to men, demonstrated stronger PFC-AMY connectivity to the relationship conflict cue compared to the neutral cue[80]. Thus, in the current study, we hypothesize that PFC-AMY functional connectivity after treatment will be greater in participants who receive ABCT+ oxytocin compared to those who receive ABCT + placebo. To test hypothesis 3, preprocessing and analysis of fMRI data will use FSL v 5.0 [81]. Preprocessing includes rigid-body head motion correction of EPI images within a run, high-pass temporal filtering (sigma = 150 seconds), geometric distortion correction, slice timing correction, spatial filtering (FWHM = 6 mm) and registration to the MNI standard brain template. ‘fsl_motion_outliers’ will be used to determine head motion outliers which will be used as a covariate of no interest in statistical analysis (together with the 6 rigid-body translation and rotation head motion parameters). The primary analysis of fMRI data will use psychophysiological interaction (PPI) modeling [82] with a seed region defined in the right AMY region from the Harvard–Oxford probabilistic structural atlas thresholded at 50%. Time series will be extracted from each participant’s right AMY using ‘fslmeants” after warping the AMY mask into each participant’s EPI space. This time series will serve as the physiological regressor for each run. The primary psychological regressors are based on the alcohol cue blocks in the alcohol run or the conflict cue blocks in the conflict run. The interaction between the primary psychological regressor for each run and the physiological regressor is the primary variable of interest.

To assess whether corticolimbic connectivity is modulated by oxytocin, the parameter estimate from the PPI interaction term will be extracted in the right and left inferior frontal cortex, opercular portion (IFC; −47, 18, 6) in each participant. The IFC regions-of-interest (ROI) are based on our preliminary study where the right AMY was functionally connected to the left IFC for the conflict cue, especially in women. In addition, the right IFC is strongly implicated in behavioral inhibition [83] and may not be activated to the same degree in participants with AUD [84]. The parameter estimates from the left and right IFC regions in each IP at pre- and post-treatment will be used in statistical analyses testing hypotheses 1 and 2 (described above). Because the hypothesized ROI may not yield the most robust response, we will also conduct a whole-brain, voxel-wise PPI analysis to identify PFC regions that show the greatest change in right AMY connectivity as a function of treatment. The voxel-wise PPI analysis will be conducted separately for each run (alcohol, conflict) and session. Group-level analyses will be carried out using FLAME 1 (FMRIB’s Local Analysis of Mixed Effects) with session treated as a repeated measure and treatment group as a between-subjects factor. FLAME2 will generate z statistical images for each interaction term

of interest. The final statistical maps will be voxel thresholded (at p = .05) and will indicate which regions show the greatest change in connectivity with the right AMY as a function of treatment and treatment group.

3. Discussion

This objective of this paper is to present the design and methodology for a Phase II randomized controlled trial examining the efficacy of intranasal oxytocin to enhance ABCT treatment outcomes. AUD is a prevalent, chronic, and debilitating condition for which few medications are approved. Several behavioral interventions, including ABCT, have garnered strong empirical support to reduce AUD symptoms, and some studies demonstrate that behavioral interventions for couples outperform individual approaches to treatment. However, a substantial number of patients with AUD do not complete treatment and continue to struggle with alcohol-related problems following treatment completion, suggesting that there is ample room to improve behavioral treatment approaches. Existing literature also demonstrates that combining behavioral intervention with medication is an effective approach to maximize treatment outcomes AUD [2,85]. To our knowledge, this is the first to examine the efficacy of a medication-enhanced psychotherapy approach for couples with AUD, and one of very few adequately powered randomized controlled trials of intranasal oxytocin among patients with AUD.

Three medications are currently FDA-approved for the treatment of AUD and most target reduction in motivation to seek alcohol (e.g., intervening at the binge/intoxication stage of the 3-stage model of addiction [86]. Given the heterogeneous nature of AUD etiology and course [87,88] and the limitations of currently available medications including non-compliance [89,90], developing new medications for AUD is a salient focus of ongoing research efforts. More recently, increased attention has been paid to medications that target brain stress systems and sensitize reward pathways to social stimuli that are commonly eroded in the course of addiction [91–95]. As described more thoroughly in the introduction section, oxytocin is a medication that has demonstrated promise to achieve this goal [96,97]. Additionally, examining the effects of medications such as oxytocin that have short (i.e., 3–4 hours) half-lives that have the specific potential to enhance within-session treatment gains is one approach that has not been examined extensively in the AUD field, although this approach has been examined more frequently for diagnoses such as posttraumatic stress disorder and anxiety disorders [60,98,99]. Further, the combination of oxytocin with an evidence-based behavioral intervention such as ABCT may help maximize compliance, optimize treatment outcomes, and reduce alcohol consumption.

Despite extensive literature demonstrating that the combination of cognitive behavioral interventions with FDA-approved medication might be the most effective treatment approach for AUD [85], all previous studies have, to our knowledge, employed cognitive behavioral interventions for individuals, not couples-based interventions. Thus, no studies have yet to examine the comparative efficacy of medication only, couples-based cognitive behavioral therapy only, and combined medication and couple-based therapy in the treatment of AUD. Notably, recent studies have found that factors that might be enhanced by primary or adjunctive couples treatment, such as coping skills and alcohol use in patients'

social network, influence outcomes by treatment approach [100,101]. Collectively, these findings suggest that the present study will make a substantial contribution to the existing literature by bridging the longstanding gap between medication-focused randomized controlled trials and those examining couples treatment for AUD. This study is equipped to measure critical factors in treatment safety and engagement including adverse events, the number of homework assignments completed during treatment, and relational factors such as psychological and physical intimate partner violence prior to and during treatment. This study is also the first to examine the effects of a medication versus placebo on within-session behaviors among couples and the extent to which those behaviors are associated with end of treatment outcomes.

This study is also the first to use a pre-post treatment neuroimaging design to examine neural correlates of treatment outcome among couples with AUD. Neuroimaging is a valuable addition to treatment development efforts, particularly in the AUD field, to examine prognostic indicators of both pharmacological and behavioral treatment response, and to characterize and clarify treatment outcomes [102–105]. In the current study, we are using a manual-guided, validated imagery script procedure to examine neural correlates of alcohol and neutral cues, and a novel adaptation of this procedure will be used to target neural responses to couple conflict directly. This is a critical advancement in the literature because couple conflict is known to influence treatment seeking for substance use disorders and engagement, and is commonly cited as a source of stress associated with alcohol use and relapse abstinence [106107,108]. Thus, this study examines subjective and neurobiological responses to all three cues at baseline, and how neural responses at baseline and end of treatment are related to alcohol and relationship outcomes. Accomplishing this goal is particularly applicable to pharmacological treatment development efforts and to the study of oxytocin specifically, as neural mechanisms of action have not yet been clearly established for this medication.

In summary, the current study employs a multimodal and interdisciplinary approach to examine the efficacy of combining intranasal oxytocin with ABCT in the treatment of AUD among couples. The primary goal is to examine whether a 40 IU dose of intranasal oxytocin, as compared to placebo, reduces alcohol use and associated problems, and improves relationship functioning during 12 weeks of ABCT therapy. The findings will inform a rapidly growing literature examining oxytocin in the treatment of various psychiatric diagnoses including substance use disorders. In addition to examining safety outcomes such as adverse events on a weekly basis, this study also examines neurobiological outcomes, changes in within-session behaviors using observational coding, and moderators of treatment outcome such as sex, which is a known correlate of oxytocin treatment outcomes in various populations [45,109]. The findings from this study will inform future research on oxytocin in the treatment of AUD, neuroimaging methodology applied to couples, and the potential translation of oxytocin to treatment settings for patients with AUD.

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Abbreviations:

ABCT	Alcohol Behavioral Couple Therapy
AMY	amygdala
AUD	alcohol use disorder
BOLD	blood oxygen level dependent
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EPI	gradient-echo planar images
EtG	ethyl glucuronide
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
IRB	Institutional Review Board
MPRAGE	magnetization-prepared rapid gradient-echo
MRI	magnetic resonance imaging
MUSC	Medical University of South Carolina
PEth	phosphatidyl ethanol
PFC	prefrontal cortex
PPI	psychophysiological interaction
TLFB	Timeline Follow Back
VA	U.S. Department of Veterans Affairs
U.S.	United States.
VAS	Visual Analogue Scale

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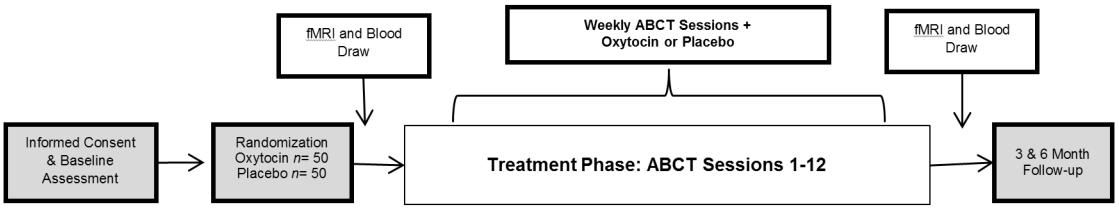

Figure 1.
Overview of study design.

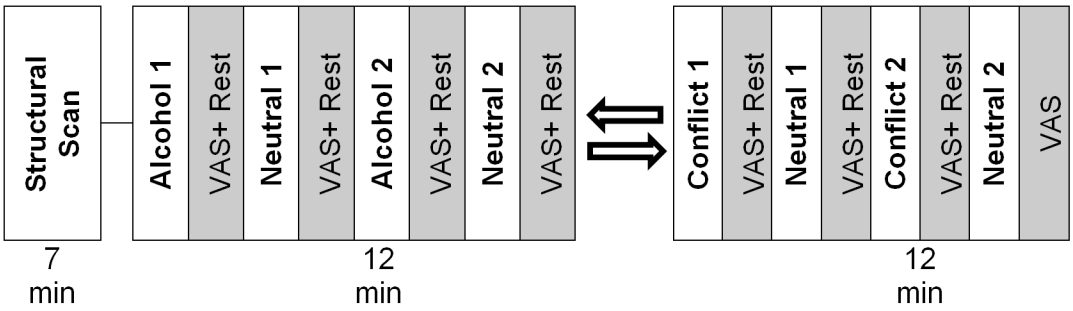

Figure 2.
Overview of fMRI session assessing response to alcohol, conflict, and neutral cues.

Table 1.

Assessment instruments and timeline.

Instrument	Purpose	BSL	Weekly	Wk 6	Wk 12	3M F/U	6M F/U
Demographics Form	Characterize sample	X					
Mini Mental Status Exam [54]	Screen for cognitive deficits	X					
MINI International Neuropsychiatric Interview [110]	Assess DSM-5 psychiatric disorders	X					
Concomitant Medications Form	Assess concomitant medications	X	X	X	X	X	X
Time Line Follow-Back [64]	**Primary outcome: AUD**	X	X	X	X	X	X
Penn Alcohol Craving Scale [67]	Assess alcohol craving	X	X	X	X	X	X
Alcohol Use Disorders Identification Test [111]	Assess alcohol problems	X		X	X	X	X
Alcohol Dependence Scale [112]	Assess domains affected by AUD	X			X	X	X
Readiness to Change Questionnaire [113])	Assess readiness to change AUD	X		X	X	X	X
Clinical Institute Withdrawal Assessment of Alcohol-Revised [56]	Assess alcohol withdrawal	X	X			X	X
Traumatic Life Events Questionnaire [114]	Assess Trauma History	X					
PTSD Checklist [115]	Assess PTSD symptoms	X			X	X	X
Beck Depression Inventory-II [116]	Assess depression	X	X	X	X	X	X
Cognitive Emotion Regulation Questionnaire [117]	Assess emotion regulation	X			X	X	X
Dyadic Adjustment Scale-short form [65]	**Primary outcome: Relationship functioning**	X	X	X	X	X	X
Revised Conflict Tactics Scale [55]	Assess intimate partner violence	X		X	X	X	X
Reasons for Violence Scale [118]	Assess reasons for partner violence	X			X	X	X
Treatment Services Review	Monitor service utilization		X	X	X	X	X
Helping Alliance Questionnaire, Therapist and Client Version [119]	Asses therapeutic alliance		X	X	X		
Treatment Adherence	Assess homework compliance		X	X	X		

BSL=Baseline. Wk= Week. F/U = Follow-Up.