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Official Title: Sex Differences, Cognitive Training & Emotion Processing

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Protocol

1. **Project Title**

   Sex Differences, Cognitive Training & Emotion Processing

2. **Investigator(s):**

   Principal Investigator: Sara Jo Nixon, Ph.D.
   Co-Investigators (Sub-I's, NIH Key Personnel): Ben Lewis, Ph.D.

3. **Abstract:**

This pilot project leverages the team's expertise in neurobehavioral assessment to examine the potential efficacy of cognitive training in treatment-seeking men and women with alcohol use disorders (AUDs). Specifically, we ask whether cognitive training interventions derived from current methods and conceptual models has differential benefits for treatment-seeking women vs. men. Although neurocognitive improvement during training is desired, of practical import is whether gains achieved during training transfer to other tasks and settings. Therefore, we also examine transfer of training gains to tasks/domains varying in their similarity to training demands. Given noted sex differences in emotional processing and the purported role of emotional factors in women's substance use, we include training engaging emotional processing via the use of affective stimuli (faces and words); predicting that women may differentially benefit from such training. We recognize that individual characteristics beyond demographics and substance use history (i.e., psychosocial variables such as interpersonal problems, mood/affect, and adaptive skills) may influence response to training and longer-term outcomes. In light of these interests and the preliminary nature of the work, equal numbers of treatment-seeking men (n=30) and women (n=30) with AUDs will be randomly assigned to one of two active training interventions (neutral or affective stimuli). To control for abstinence-related recovery, a third group of participants (here Subjects, Ss) (n=30), meeting identical selection criteria, will complete pre and post-intervention testing, but will not undergo the training intervention. Ss will complete baseline assessment, up to 12 training sessions (for active groups) and post-intervention testing (~2-3wks after baseline) and will be contacted monthly for 3 months after discharge .

4. **Background**

Neurobehavioral Concomitants of Chronic Substance Misuse. Although the chronic excessive use of numerous licit and illicit substances is known to impact brain and cognition [e.g., 1-3], the prevalence of AUDs in the general and treatment-seeking populations has directed a large literature on alcohol's neurotoxic effects. Thus, within this application, we focus on the neurobehavioral consequences associated with significant AUDs (herein, alcoholics). While noting considerable heterogeneity between studies and across specific tests, research reveals alcohol-related neurobehavioral compromise in a wide range of neuropsychological domains [e.g., 2-4], neurophysiological indicators [e.g., 5-7], brain activation patterns and measures of structural integrity [e.g., 8-9]. Importantly, alcohol plays a critical role in neurobehavioral integrity even among polysubstance abusers [10-11, see also 12].

Recent work has shifted from detailing specific tasks vulnerable to chronic, excessive alcohol use to focusing on component processes that may underlie performance across tasks/domains. Among these, processes underlying attention and working memory are particularly noteworthy. Essential to effective attention and working memory are the top-down control processes of enhancement and suppression. Enhancement refers to the ability to respond/attend to relevant stimuli whereas suppression refers to the ability to respond appropriately to irrelevancy, i.e., the ability to ignore irrelevancy [13-15]. We have previously referred to the inability to effectively suppress or inhibit response to irrelevancy as a deficit in efficiency and proposed that it was a critical factor underlying alcohol-related compromise [16-18]. On-going work by our team and others supports the conclusion that this deficit accounts for substantial, albeit not all, variance in alcohol-related compromise [11;19-21].

Inclusion of Women. With notable exceptions, research through the early/mid-1980's was conducted in predominantly male facilities with relatively little impetus for the inclusion of women [but see 22-23]. Once initiated, mixed sex and female-specific projects *generally* reported that alcoholic women were compromised across similar domains and to a similar, or greater, extent as were alcoholic men, relative to sex-specific

controls [24-28]. Furthermore, alcoholic women typically reported less intense and/or shorter drinking histories than men. Thus, it was commonly concluded that women were more vulnerable than were men to alcohol's neurotoxic effects [29-31]. However, continuing work has not consistently observed this sex-related vulnerability in regard to alcohol's neurobehavioral consequences [32-34].

Relatedly, although women are now recruited for the majority of published studies, numbers are often insufficient to allow analysis of sex main or interaction effects [for issues see 34]. Thus, women remain, as referenced in the PA and reflected in NIH's recent notice regarding sex as an essential biological factor, grossly underrepresented in addiction science. Without adequately designed, systematic study, the neurobehavioral consequences of AUDs and other SUDs among women will not be fully appreciated and thus cannot be appropriately addressed.

Summary. AUDs are associated with significant compromise across a range of neurobehavioral domains. Conceptual and methodological advancements have shifted focus from detailing the effects of chronic alcohol on specific tests to exploring compromise in processes that may underlie performance across tasks/domains. Through this effort, suppression, a top-down control process essential to constraining attention and facilitating working memory, has demonstrated utility as a significant neurobehavioral mechanism underlying alcohol-related compromise. Despite conceptual advances, the implications of these findings are significantly constrained by the under-representation of women.

Neurobehavioral Recovery. Importantly, recovery of function with sustained abstinence can be anticipated [35-37]. However, recovery is uneven across domains and specific domains such as those related to executive function may require months to years [38-40]. Whether men and women differ in the pattern and degree of recovery remains controversial and conclusions are limited by small sample sizes and inconsistent analysis of sex differences [27;31;33;37;41;42]. Thus, there remains a need for focused study on sex differences in recovery.

The possibility of using cognitive training/rehabilitation to facilitate early recovery among treatment-seekers was discussed in earlier decades [43-45]. However, the propositions failed to engage systematic study or widespread acceptance. Factors such as cost and staffing as well as inconsistent findings regarding the relevance of neurocognitive abilities assessed in treatment to eventual outcomes may have contributed to the reticence [46-49].

Although largely unexplored for decades, there has been a resurgence of interest in the potential benefit of cognitive retraining for the addictions [50-52]. Current guiding frameworks focus on the role of bias modification and executive functions, such as cognitive control [53-55]. While the training procedures/methods differ, the models are derived from the assumption that retraining of attentional/working memory processes (which in turn are related to executive function) can lead to not only improved cognitive performance but also to more effective control of alcohol or drug use behaviors. While there is value in cognitive bias modification [54-55], given our on-going work and the constraints of the R03, we focus on attention/working memory processes wherein preliminary studies report positive outcomes in modulating problematic alcohol use [56-57]. Of particular relevance to our work is the fact that success in these studies centers on modifying response to irrelevancy, i.e., reducing inefficiency by improving suppression processes. Importantly, outcomes in these studies were assessed only through the immediate treatment period [57] or to one month beyond the intervention [56]. This limitation reflects the early phase of study. To our knowledge, analyses of sex differences have not been reported [but see 58].

A core issue for cognitive training strategies is whether improvements seen during training impact performance in other settings; i.e., do training gains transfer beyond the training tasks/context [59-61]. Although it is expected that performance will improve with challenging practice (i.e., gains), the larger question is whether these gains transfer to other tasks varying in the degree to which they rely on common processes. Many programs have produced disappointing outcomes [61, but see 57]. However, the studies cited above [56-57], reporting a reduction in substance use (i.e., enhanced control) following training, illustrate meaningful transfer. Another transfer dimension, the transfer of training between tasks differing in stimulus qualities, i.e., neutral or emotional/affective, was examined by Schweizer and colleagues [60;62]. Recognizing that improved processing of emotionally valent stimuli could benefit real-world interactions, she

and her colleagues examined this question in young adults. They used a challenging dual n-back working memory training task, and varied the task stimuli between groups (affective vs. neutral stimuli). They found that gains on an emotional (i.e., faces and affective words) Stroop transfer task was improved only in the group trained with affective stimuli.

Importantly, deficits in emotion processing are commonly reported in persons with AUDs [63-68]. Although understudied, it is likely that these deficits are relevant to long-term adaptation and recovery [e.g., 64; 69-73]. Furthermore, even though there are noted sex differences in emotion processing [74-76] and emotional/interpersonal dynamics are frequently implicated in women's drinking [77], both sexes show impaired/ dysregulated responding [e.g., 73;78]. Thus, if cognitive benefits achieved during training could be applied to the processing of affective/emotionally relevant contexts, long-term outcomes might be further enhanced for both sexes.

Summary. There is renewed interest in determining whether cognitive retraining directed to enhancing performance on underlying component processes may improve the effectiveness of treatment for SUDs. Current studies offer promise and suggest directions for additional research. This project is designed to address two areas of clinical and scientific relevance; the systematic inclusion of women and the extension of training paradigms to consider transfer of gains to tasks engaging emotion processing. Additionally, given the limited data on longer-term effects, we will extend the follow-up to cover the first 90 days following discharge, i.e., through a known period of heightened vulnerability [79].

Overall Summary. Neurobehavioral deficits are common in treatment-seeking persons with AUDs. Cognitive training directed to commonly compromised processes shows promise and merits further research. As a pilot project, the scope of work is necessarily limited. In this application, we seek to extend current work by examining sex differences in response to cognitive training in attention/working memory and by investigating whether training engaging emotion processes differentially affects outcomes, and if the sexes differ in their response to this training. We will also examine relationships among demographic variables, comorbid substance use, performance gains, and post-treatment outcomes (i.e., over a 3 month period), thereby providing direction for consideration of individual differences in training outcomes. Together these data will inform questions of feasibility, identify potential subgroups (beyond sex) varying in response, and guide the development of a more comprehensive R01 application assessing cognitive training among treatment-seekers with AUDs.

5. Aims (**H**=hypothesis, **E**=empirical question)

Aim 1: Investigate potential sex differences in response to cognitive training. In the absence of a consistent literature, we ask: **E1:** Will men and women show differential transfer of gains in post-intervention testing? **E2:** Will transfer of gains for men vs. women differ on the basis of transfer task demands? **E3**: Will they differ in the degree to which they demonstrate improvement across training? **E4**: Will the relationship between baseline performance, training gains, relapse and/or post-treatment adaptation differ for women and men?

Aim 2: Determine whether stimulus characteristics (neutral vs. affective) define transferability of gains and/or training trajectories. Given current literature, we predict that; **H1**: Active training, regardless of condition, will produce greater performance gains than the control condition, **H2**: Training with affective stimuli as opposed to neutral stimuli will differentially benefit performance on transfer tasks engaging affective stimuli, and, **H3:** Training gains will be more readily transferred to tasks engaging highly similar cognitive demands (processes) vs. more general processes. We ask, **E5:** To what extent do training trajectories vary as a function of training stimulus characteristics?

Aim 3: Explore sex by training condition interactions. Existing studies suggest that: **H4**: Training with affective stimuli may differentially benefit women as compared to men, although we expect that both sexes are likely to show transfer of gains within the affective condition (**H5**). We ask, **E6**: Do training trajectories vary by sex? **E7:** Are training trajectories subject to the sex by condition interaction?

Secondary/Exploratory Aims: The study provides the opportunity to examine relationships between/among a variety of individual characteristics beyond those treated as key covariates, e.g., age, education, alcohol use history, that may impact the efficacy of training interventions, e.g., pre-treatment levels of functional adaptation, mood/affect during treatment, and comorbid substance use. These associations will be examined in exploratory analyses relying on correlational methods and will inform future projects. Similarly, Ss acceptability of the intervention will be assessed through preliminary methods and will be considered in structuring future interventions.

6. Research Plan

The primary design is a 2 (Sex) by 3 (Training Condition: Neutral, Affective, Control) by 2 (Time: Baseline, Post-training) mixed design. The control Ss will meet identical selection criteria but complete only baseline and retesting, controlling for abstinence-related improvement. R03 limitations prohibit the inclusion of an active control condition [56]. Follow-up phone interviews allow preliminary assessment of the impact of cognitive training on post-treatment functioning. Cell sizes (Table 1) were informed by power analyses and the constraints of the R03 mechanism [see Data Analysis]. Assignment to neutral vs. affective training group will be randomized within sex. To minimize confounds associated with conducting active interventions and control conditions concurrently within the facilities (i.e., Ss being unwilling to serve as controls due to differential compensation), ~ half of the control Ss will complete participation at the initiation of the project and ~half after training groups have been recruited. Further, separate ICFs are utilized, with control ICFs remaining unlabeled (i.e., not referred to as a "control" group).

Condition:	Sex:		
	Men	Women	Total
Neutral	*15*	*15*	*30*
Affective	*15*	*15*	*30*
Control	*15*	*15*	*30*
			90

Table 1: Overall Study Design

The overall structure of the intervention involves baseline cognitive assessment including performance on the standard and emotional Stroop, 3 weeks of training on neutral or emotional versions of two tasks with strong demands on attention/working memory (specifically the capacity to suppress response to irrelevancy) and retesting on the cognitive battery and the emotional and standard Stroop. The primary dependent variables are differences between pre- and post-intervention performance on the two Stroop tasks as a function of training condition (including neutral, affective and control), sex, and their interaction. Ss complete a neurocognitive battery at baseline, affording an additional test of improvement and transfer of gains through re-administration after training.

Participant (Ss) Selection Criteria. Ss are recruited from treatment facilities in north central FL with expected length of stays extending across the intervention period. Ss range in age from 25-65 with a minimum of 10 years of education. Ss may not have medical or psychiatric histories which would confound participation or data interpretation, e.g., epilepsy, stroke, untreated hypertension, psychotic disorders, anxiolytic medications, etc. Endorsement of suicidal intent is exclusionary, and is reported to facility clinical staff. Comorbid substance use including nicotine use is not exclusionary and is addressed using both categorical and continuous measures. Ss are not selected by race/ethnicity (~69% Caucasian, 28% African American;7% Hispanic).

Screening. After providing informed consent, Ss complete questionnaires related to general health, substance use history, and mood/affect. Recent alcohol use is quantified using quantity/frequency measures adapted from Cahalan et al., [82]. Nicotine dependence is ascertained using the Fägerstrom Tobacco and Nicotine Dependence [FTND; 83] measure. Other substance use is queried in regard to chronicity, quantity, and frequency. Mood/affect are assessed with the Beck Depression Inventory-II [BDI-II; 84] and Spielberger State Anxiety Inventory [AI; 85]. Family history for alcohol or other drug use is assessed using a modified family tree [86]. Ss then complete selected modules from the Structured Clinical Interview for DSM-5 (SCID-5) [81]. Ss receive $20 for completing the screening questionnaires and $10 for completing the structured interview. Reimbursement is pro-rated if Ss discontinue or are disqualified prior to completing. Data will be used in descriptive and post-hoc analysis to examine potential subgroups and/or covariates, as appropriate.

Baseline Assessment. This assessment will include administration of the cognitive efficiency battery, re-administration of the BDI-II and AI (applied during screening), and administration of the emotional Stroop task. Ss will receive $25 for completion of baseline assessment.

Cognitive Efficiency Battery. The battery utilizes paper/pencil and computerized tasks including Trail-Making Task A/B [89], Digit Symbol Substitution Task [90], Little Man Task [91], Visual-Perceptual Analysis Task [91], Wisconsin Card Sorting Task [92], Sternberg Short-Term Memory Task [93-94], and the standard Color-Word (standard) Stroop Task [95-96]. A simple reaction time task quantifies gross motor function. By including tasks with varying dependence on attentional processing/working memory, the battery enables separation of improvement/transfer of gains into process-specific and generalized effects. Accuracy (ACC), reaction times (RT), and the efficiency ratio (ACC/RT), for individual tests and the overall battery, are derived, as appropriate. *Time: ~25 min*

Emotional Stroop. We utilized the emotional Stroop task reported by Schweizer et al [60]; developed by Preston & Stansfield, 2008 [97] as a primary measure of training effects. Emotional stimuli are words overlaid on faces from the Pictures of Facial Affect stimuli set [PFA; 98]. Words are centered horizontally within the frame and vertically at vertical midpoint of the nose. Words are presented at 25% opacity (Fig. 2). Ss are instructed to respond to the *word* presented as quickly and accurately as possible. Ss respond to the word by pressing a corresponding response key. Three responses are possible: HAPPY, SAD, and ANGRY. Ss respond with their dominant hand on labeled keyboard keys. The overlaid words were taken from a list of eight emotion adjectives prototypical of the three emotional response categories [99; see Appendix]. Trials will consist of congruent (word and face have matching emotions), incongruent (word and face expressions do not match), and neutral (neutral face) conditions. Four emotions (HAPPY, SAD, ANGRY, NEUTRAL) from four actors in the PFA set will be used (2 men; 2 women). The combination of these 16 facial stimuli and 24 adjectives creates a pool of 384 unique stimuli. From this pool, Ss will view 192 congruent stimuli, 96 neutral stimuli, and 96 incongruent stimuli (384 total trials). The higher proportion of congruent trials are used because Stroop effects (>RT on incongruent trials) are known to be sensitive to habituation. No stimuli will be repeated more than once. Stimuli will remain on the screen until Ss respond or 5 secs have elapsed (resulting in an omission). A colored (red/green for correct/incorrect) border provides accuracy feedback. Schwiezer's timing of 500 msec for feedback and ITI will be tested and adjusted, as needed, during task development. Dependent variables will include RT, ACC in each emotion/congruency condition, and efficiency (ACC/RT), with particular interest in the incongruent conditions. *Time: ~15 min.*

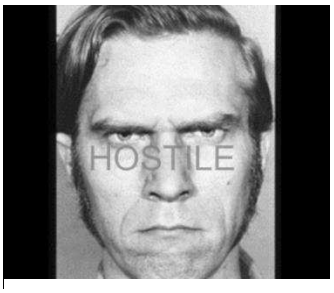

Fig 2. Example of a congruent trial w/congruent word & facial emotion

Cognitive Training. Training will be conducted over up to three weeks at the treatment facility. Training will involve performance-based progression, an important characteristic of effective training [56; 60]. We will use the dual n-back as reported by Schwiezer et al [60] and a modification of a directed attend/ignore tasks used in our prior work [e.g., 100]. Ss will be instructed to complete twelve training sessions over three weeks (4/week), each lasting 45-50 min. Ss completing 2 or fewer sessions in the first week or withdrawing during this time will be discontinued from study and replaced. Drop-outs after the 1st week of training will not be replaced. The number of sessions completed/week will inform future study development and will be used as a descriptive variable and in covariate analyses, as appropriate. Given study objectives, compensation will be provided on a daily basis ($15/session), with a bonus for completing at least nine sessions ($20 for sessions 9-12). Study staff will be present for all training to ensure S identification, assist with software issues, provide compensation, and ensure data integrity. Throughout training, one group will train with versions of the tasks using emotionally-laden stimuli (Affective Training Group); one group will train using emotionally-neutral versions of the tasks (Neutral Training Group). To parallel Schwiezer's work and given alcoholics' deficits in the processing of negative emotion [65; 71; 101], affective stimuli will reflect negative states. All face models will be presented an equal number of times across affect categories (i.e., no individual face actor will appear more often as "angry" than "fearful").

Training sessions. Although treatment facilities are smoke-free, several provide areas for smoke breaks. Therefore, Ss will be informed during consenting and reminded prior to the training session that smoke breaks will not be allowed during training and advised to have their last smoke within an hour before each training session. At the initiation of each session, Ss will provide information regarding time/quantity of last nicotine use. These data will be used in descriptive and covariate analyses, as appropriate. To provide pilot data regarding training acceptability and presuming that acceptability may vary with progress, after each

session, Ss will indicate on a visual analogue scale the degree to which they found the tasks a) tiring, b) boring, c) engaging, d) effortful, e) enjoyable, and f) stimulating. Ss are asked to rate degree of improvement and indicate if they would recommend similar training to others. These data will be used as descriptors and may aid in directing future interventions. Finally, training task order will be counterbalanced to mitigate sequencing effects. [See Appendix for additional training task detail]

Dual n-Back Task The dual *n*-back task [60] involves both auditory and visual cues. Ss are presented with a 4 x 4 grid. A face is presented in one of the grid tiles, while an auditory stimulus (a single word) is delivered simultaneously via headset (Fig. 3). Ss indicate whether the position of the visual stimulus OR content of the auditory stimulus matches that of the trial "n-back"; e.g., if n=1, Ss indicate if current stimuli match those from immediately preceding presentation. For visual stimuli, Ss are instructed to ignore the content of the image and attend to the location in which it is presented. One training session includes 20 blocks of 20+*n* trials. Twelve target trials (6 per modality) will be included in each block. Training begins at *n*=1. The *n*-back designation changes dynamically with Ss performance. After each block, if Ss make < 3 errors, *n* increases by 1; if > 5 errors are made, *n* decreases by 1. Otherwise, *n* remains the same. Due to its manipulation of bimodal stimuli, the task places a high demand on executive control processes, limiting the development of task-specific strategies. Schweizer et al. [60] found that college-aged controls progressed from a mean of ~4.5 *n*-back at initiation to ~6.5 *n*-back over 9 training days. Baseline performance among our Ss is unlikely to be this high. However, observable improvement should occur across the 12 sessions. Should pilot data indicate that the dual modality task is subject to floor effects, we will shift to a visual modality with combined cues. *Time: ~20-25 min/day.*

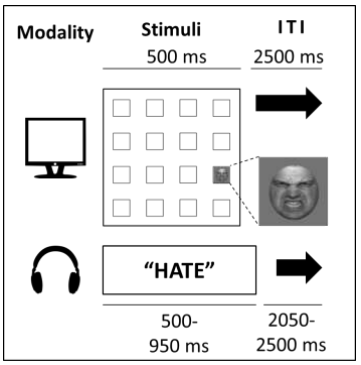

Fig 3. Modified from Schweizer et al., 2011. Each trial (Stimuli + ITI) = 3000 msec

Directed Attend/Ignore Task Ss will also train on a task developed by Gazzaley et al. [13] to examine top-down control processes directing selective attention and modified from our previous work [100]. Ss are directed to either "Remember faces but ignore scenes" or "Remember scenes but ignore faces". [See Fig. 4]. Following a delay, a probe stimulus is provided (either face or scene, depending on instructional set) and Ss indicate via button press whether the probe stimulus matched the presentation stimuli. Each training session will include 4 blocks (2 per instructional set) of 20 trials. The duration of stimuli presentation and delay intervals used at training initiation are depicted in Fig 4. Task difficulty will change dynamically with Ss' performance with improved accuracy resulting in extended delay time and shortened stimulus presentation.. *Training Time: ~25 min/day*

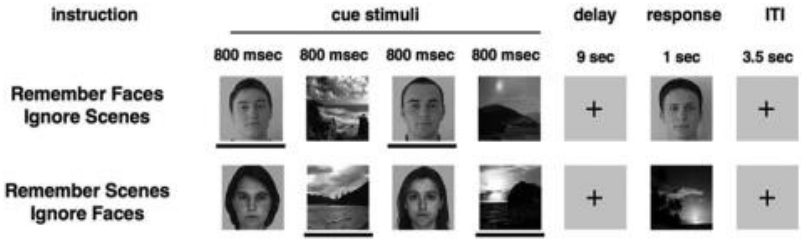

Fig 4. Modified from Gazzaley et al., 2008. Lines below the cue stimuli reflect task relevance for illustration and are not present during task administration.

Post-Training Assessment/Retesting. Within 1-5 days following training completion (dictated by discharge dates), Ss will be re-administered the BDI-II, AI, the emotional Stroop, and the cognitive efficiency battery. Time: ~ 1 hr. Reimbursement: $25.

Follow-up. Follow-up interviews are conducted approximately 30, 60, and 90 days following treatment discharge (or post-training assessment, for outpatient participants). Interviews use the Project MATCH's modification of the timeline follow-back [TLFB; 102, 103] for assessing quantity and frequency of daily substance use (alcohol, nicotine, other drugs) over the previous month. Ss also complete the "Your friends and family" items from Moos' Health and Daily Living Scales [104]. The Profile of Mood States (POMS) 2-A Short [105] and Mini Alcohol Craving Experience questionnaire [107] will also be administered. Ss receive $20 for each completed follow-up interview. Estimates suggest that ~ 60% of the sample will complete all interviews. *Time: ~30 min.* [See Appendix for listing]

Data Analysis Strategy. *General considerations:* Statistical analyses will apply SAS Version 9.4 (SAS Institute). Data will be examined for completeness, outliers, and distributional fit with transformations employed, as appropriate. Descriptive statistics, graphical methods and correlational matrices will be used to characterize the data. To examine outcomes over time generalized linear mixed models (GLMM) and linear contrasts will be used. Dependent variables are noted in task descriptions. Aims 1-3 are addressed in both transfer and training analyses. *Feasibility:* The design should minimize dropout, however we will evaluate dropout rates and the number of trainings completed prior to dropout as a function of sex, training condition, and the interaction. For selected analyses, missing data techniques will be employed; pattern-mixture models based on point of loss and sensitivity analysis will aid in interpretation. *Transfer effects:* GLMM analyses will be employed to examine effects of training condition, sex, and their interaction on transfer task performance. Dependent variables include RT, ACC, and efficiency (ACC/RT) for each Stroop condition (congruent, incongruent, neutral) and the cognitive battery. *Training Effects:* Linear contrasts will be utilized to compare performance on the training tasks across training session, group, and sex. We will explore whether the two training tasks are differentially related to transfer of gains. Secondary aim: Exploratory methods will be applied to a) examine associations between/among measures of functional adaptation, mood/affect, transfer gains and post-treatment substance use, and b) explore potential subgroups/subtypes that vary in response to training and/or post-treatment outcomes. Training session ratings of acceptability and perceived improvement will be compiled to provide proxy indicators of engagement to inform training session development. *Power*: Schweizer et al. [60], report large transfer effects (Cohen's f's, .82-1.10) but do not address sex differences. Given the developmental nature of the investigation and the intent to identify preliminary data regarding sex differences meriting further study, we will consider sex main effects at α =.10. With an estimated moderate effect size (Cohen's f=.25) and a correlation between measures of rho=.5, our power to detect sex effects is .78. Our power to detect transfer effects relative to controls is 1.0 with power =.98 to detect more modest between-group training effects (Cohen's f ~.40; α =.05). For the critical interaction of sex and training condition, and estimating a moderate effect, our power is .96 (α =.05, rho =.5). This estimate fails to account for Ss dropout. Absent guiding estimates, we conducted an analysis with a dropout of 10 Ss/ condition and maintained power =.80.

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7. Possible Discomforts and Risks

*Selection criteria*Detoxified alcohol dependent Ss (N=90; 45 women) will be recruited from inpatient, residential and intensive outpatient alcohol/drug treatment facilities across north central Florida. Ss will be between 25-65 with a minimum of 10 years of education. Ss will have completed medical detoxification (if it was required) and be abstinent from psychoactive drugs used to manage withdrawal symptoms. Only Ss reporting chronicity of alcohol problems ≥ 5 yrs will be recruited. This threshold has not unduly compromised recruitment in previous work with this population. Given the reported rates of cigarette smoking in our treatment populations (~88%), current and past smoking history will be queried and data will be used in descriptive and correlational analyses.

Due to the nature of this work as a pilot/feasibility study, exclusionary criteria primarily reflect conditions which would confound data interpretation or limit subjects' ability to participate Ss will be excluded if reporting histories of a) significant neurologic insult (e.g., epilepsy, stroke), or b) medical disorders which would confound data interpretation or c) the on-going use of medications which could compromise testing (e.g., specific antihistamines, benzodiazepines, narcotic pain medication, etc.).Ss will also be excluded from study if reporting current diagnosis for any psychotic disorder (e.g., any of the schizophrenic disorders or psychotic depression), current/unremitted panic disorder, or bipolar disorder. Consistent with IRB guidance and facility preference, reasons for the S's exclusion are not revealed to clinical staff.

Ss provide written, informed consent prior to completing any screening, assessment, or training procedure. They are paid for their participation in each project phase (individually for screening, assessment, training, and follow-up).

Should Ss indicate suicidal intent on the Beck Depression Inventory-II, during administration of the SCID-5, or through incidental communication, clinical staff are immediately notified and Ss are discontinued from study. For other psychiatric issues, Ss are asked if they have discussed these issues with clinical staff. If they have not, they are encouraged to do so. However, only in the case of intent to commit suicide or injure another (including child or elder abuse) is the confidentiality of the test session breached (i.e., immediate contact with clinical staff). No direct inquiry regarding intended or historic injury to others is made. Thus, this

information would be revealed only through incidental communication. This possibility is explained verbally and in the informed consent

Sources of material. All data are coded by alphanumeric code independent from any personal identifiers. Data are reported in such a way that the identity of Ss cannot be discerned from the database. No biospecimens are collected.. Only research staff completing HIPAA, local IRB and NIH training regarding human research will have access to individually identifiable private information from Ss.

Potential Risks. The primary risk is a violation of confidentiality. To reduce this risk, all data are coded by alphanumeric code and are scored, filed, and retained in a manner designed to facilitate confidentiality. Data and consent forms are kept in separate locked files and subject numbers do not appear on consent forms. The code linking the name and number is retained on a UF encrypted and password protected file. This link is not stored with study data. The link is destroyed at the end of study. Ss participating in the follow-up component may complete the interviews in the lab or by phone. Regardless, follow-up information is coded only by subject number and will not include personal identifiers. A second risk is that Ss may also experience some discomfort in responding to some of the questions or fatigue during testing. The assistants are carefully trained regarding the sensitivity of these questions, frequently reminding Ss of the confidential nature of this information and the opportunity to skip questions if they are too uncomfortable. In the hundreds of interviews conducted in our previous and on-going NIH grants, these interviews have been conducted without incident. To reduce fatigue, R03 training sessions are completed in ~45 min.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent: Ss will be recruited from substance abuse treatment facilities through in-person announcements by trained research assistants from our laboratory. Potential Ss express their interest directly to our research assistants, who describe the study, and then, if Ss are interested, initiates the informed consent process. Ss are reassured that their decision regarding participation will not impact their clinical care.

Ss will be provided a full description of the assessment and training components of the study prior to participating, enabling them to review it with friends/family/peers prior to their initial assessment. As noted elsewhere, research assistants are trained in seeking informed consent (through both IRB, NIH and PI directed training).

Protection Against Risk: To protect privacy, individuals complete the screening packet in an area separate from clinical activities with the aid of trained research assistants. The SCID-5, baseline assessment, computerized training, and post-intervention assessment are administered in designated rooms at the treatment facilities. To protect against potential breaches of confidentiality, data are coded by a number unrelated to the subject and cannot be directly connected to individual Ss. Data are reported in aggregate form wherein no individuals can be identified, and stored on the Department of Psychiatry's encrypted and password-protected server. Additionally, Ss are protected by a Certificate of Confidentiality.

Ss may withdraw at any point in the screening, testing, or training sessions without impact on clinical care. If Ss discontinue during the conduct of the active study, they receive prorated compensation. Follow-up interviews are reimbursed after each completed interview.

8. Possible Benefits

Individuals in the training groups may experience some improvements in cognitive performance.

9. Conflict of Interest

There is no conflict of interest beyond the professional benefit from academic publication or presentation of the results.

DATA AND SAFETY MONITORING PLAN (approved by NIAAA)

The demonstration/pilot project involves the recruitment of otherwise healthy men and women seeking treatment for a substance use disorder. Individuals with medical or comorbid psychiatric disorders that would confound interpretation of neurocognitive function are excluded from study. Depending on the phase of the project, qualifying and consenting participants are assigned to the control group, or randomly assigned to one of the two active computerized training groups (affective vs. neutral), with the constraint that every attempt is made to recruit equal numbers of men and women across the three groups. Cognitive capacity is assessed prior to the intervention and tracked across the intervention (multiple sessions across multiple weeks). After the intervention, all participants are contacted by phone and provide feedback regarding post-treatment drinking and psychosocial adaptation at three time-points (30, 60, and 90 days post-treatment). The intervention does not involve the administration of alcohol or any other drug or pharmacological agent.

1. **Reporting and Monitoring of Adverse Events**. AEs, regardless of severity will be defined by FDA and local IRB standards. Every serious adverse event (SAE), as determined by the PI, Sara Jo Nixon, Ph.D., will be reported to both the University of Florida Health Science Center Institutional Review Board (IRB-01) and the NIAAA project officer within 48 hours. In addition, a summary of all adverse events, regardless of severity, will be submitted to both the NIAAA project officer and IRB-01 on an annual basis. Given selection criteria and the study protocol that involves only participation in "brain-training" or cognitive practice tasks, no SAEs are anticipated. The most common events are likely to be fatigue and/or headache. The protocol is designed to mitigate the probability of each with breaks, etc. Headache will be reported in real-time to the participant's counselor on-site, or his/her designee, to ensure appropriate intervention. All events will be reviewed during weekly staff meetings including research staff, graduate research assistants, and the PI. Should a pattern of adverse events be detected, the protocol will be re-evaluated and amended, as appropriate.

2. **Follow-up**: The intervention is complete at the time that the cognitive training concludes (within three weeks of initiation). One of the objectives of the study is to examine to what degree cognitive abilities and/or their improvement during training and early recovery may support post-treatment abstinence and recovery. In phone interviews, using established instruments focusing on substance use, current mood, and psychosocial adaptation, participants provide information at 30, 60, and 90 days after discharge/intervention. This study is not a direct intervention study and thus will not provide direct referral to treatment. In the event that persons indicate that they are a threat to self or others, we will provide referral mental health information. Additional action may involve a follow-up phone interview, direct referral to a mental health facility and/or Emergency Department, or the involvement of other authorities, if a direct threat is issued. In our history, we have not had to use these latter options, but they are available if needed.

4. **Data Quality Assurance and Confidentiality**. Participant data will be given an alphanumeric code independent of personal identifiers. The "key" to this code will be stored securely in an encrypted, password-protected database on the restricted-access servers of the Department of Psychiatry. Trained research assistants will hand-enter all data from pencil/paper tasks and questionnaires into REDCap (Research Electronic Data Capture, Vanderbilt University). The REDCap system will have protected health information tagged for de-identification of data. REDCap provides a means of data verification using second entry that is will be applied to ensure accuracy. Discrepancies not linked to direct error (i.e., interpretation) are resolved through review of data, and consensus derived through staff review. To provide greater confidentiality, we have obtained a Certificate of Confidentiality from the NIH to cover data obtained throughout the project.