

Study: Cognitive Enhancement through Computerized Training

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Protocol

1. Project Title

Cognitive Enhancement through Computerized Training

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3. Abstract:

Programmatic investigation of neurocognitive functioning in alcohol use disorder (AUD) has revealed widespread and sustained impairments. Despite conceptual relevance to treatment efficacy, few AUD interventions have been directed to the remediation of these impairments. The current project is responsive to this gap. The current project investigates the efficacy of two experimental cognitive training interventions in a sample of inpatients in treatment for AUD. While the effectiveness of CT to enhance function is supported by diverse literatures, it remains largely unexamined in AUD. The current project will interrogate the degree to which cognitive training interventions can “transfer” cognitive gains to untrained tasks/domains, and improve overall executive functioning. It will apply conceptual models from the CT and alcohol literatures to identify factors associated with CT efficacy. The impact of cognitive training on functional outcomes, including post-discharge drinking, will be investigated. Finally, relationships between cognitive recovery during treatment and post-discharge adaptation will be examined. Thus, this project will be of substantial import to public health, alcohol science, and will inform future intervention efforts.

4. Background

Neurocognitive Deficits Neurocognitive deficits are common in alcohol use disorder (AUD). Although heterogeneous in nature and severity, current estimates indicate 50%-80%, of alcoholics are affected [4]. A substantial literature utilizing diverse neurobehavioral measures [5] has elucidated widespread impairment across visuospatial, memory, executive, and psychomotor domains (for recent reviews see [5-7]). Despite the plurality of affected processes, deficits in executive functions directing the controlled, effortful processing and manipulation of novel information are among the most common [8-16]. Consistently, frontal lobe structures subserving these functions display particular vulnerability to alcohol insult [17-20]. *Pervasive AUD-associated disruptions in executive functions suggest their utility as targets for neurocognitive intervention, particularly when considered alongside their conceptual role in treatment outcomes and their capacity for recovery.*

Neurocognitive Recovery Neurocognitive deficits display time-dependent recovery during abstinence. Cross-sectional investigations suggest substantial short-term (~1 month) improvements followed by more modest mid-term (~1 year) gains, but commonly reflect incomplete restoration of function [21] relative to healthy community comparison groups (controls). Fein and colleagues report differences in structure [22] and function [23] persisting after six years of sobriety. Domain-specific differences in recovery trajectories are noted; working memory displays typical short- to mid-term gains [10,24,25], while attentional deficits are slower to recover, with some studies observing no short-term gains (e.g., [26]). Difficulties in accounting for

pre-morbid differences between alcoholics and controls somewhat limit cross-sectional analyses, potentially contributing to the insufficient characterization of recovery in processes critical to treatment outcomes, including inhibitory control [21].

Longitudinal analyses are sparse, although investigations by Parsons (e.g., [27,28]), Sullivan & Pfefferbaum (e.g., [29]), and Bates ([30,31]) provide notable exceptions. This work reveals marked heterogeneity in recovery trajectories and highlights the substantial difficulty in their prediction (e.g., [30]). Non-modal trajectories are common, and critically, *a substantial proportion of alcoholics fail to display short-term recovery* [31].

Treatment Outcomes Education and skill development are integral to AUD treatment and require the processing, memorization, and implementation of novel information. Cognitively impaired alcoholics learn fewer treatment-related skills [32,33] and recall less treatment-relevant information ([34-37]). Impairments may also impede treatment through lower self-efficacy [38] and readiness to change [39]. However, relationships between cognitive function and abstinence outcomes are complex; one investigation using the Project MATCH sample revealed countervailing impairment effects, including enhancement (e.g., support-seeking) and disruption (e.g., noncompliance) of treatment processes [38]. These observations were restricted to impairment measured at treatment entry, limiting their capacity to inform hypothesized benefits of neurocognitive recovery to treatment outcomes. Buckman et al. [40] observed increased post-treatment substance use among individuals with diminished recovery of executive function during treatment, but this was restricted to individuals with low abstinence-promoting social support. *Importantly, no empirical studies have assessed the impact of neurocognitive interventions on treatment outcomes.*

Cognitive Training Cognitive training aims to promote neurobehavioral or neurophysiological alterations through repeated engagement of cognitive processes under conditions of sufficient difficulty that neural resource limits are taxed. This process-oriented approach demonstrates efficacy to transfer gains in performance or neurophysiological efficiency to novel tasks engaging the trained process, or “proximal transfer” (for review see [41]). Provocatively, gains in untrained processes/tasks, or “distal transfer”, are also demonstrated among both impaired (e.g., [42]) and healthy (e.g., [43]) individuals. Distal transfer effects in healthy, high-functioning adults are less common, suggesting a “ceiling effect” for CT enhancements (for negative findings & discussion see [44]). Although equivocation remains concerning the longevity and sample specificity of transfer effects, findings have driven significant clinical interest regarding addiction treatment [45-47]. Current evidence strongly supports the prevailing hypothesis that transfer depends on the extent to which trained and untrained processes rely on common neural networks [41,48]. Thus, targeting processes that elicit widespread functional connectivity of diverse networks is a common strategy, exemplified by working memory (WM) approaches.

Working Memory Training Under sufficiently challenging conditions, efficient WM requires integration of broad cortical and subcortical systems. Frontally-mediated attentional and inhibitory executive control mechanisms direct attention and suppression of task-relevant and irrelevant information [49,50]. Temporally-mediated systems traditionally thought to subserve “long-term” memory are engaged when WM capacity is taxed [51]. Coordination between these systems, parietal networks commonly associated with WM, and others (e.g., motivational, somatosensory) depend on thalamic integration [52]. While these examples insufficiently describe the extent of WM-associated activation, they illustrate the diversity of potential transfer effects following WM training. This diversity is supported by observed gains in episodic memory [53], discounting of delayed rewards [54], attention [43], processing speed [55], fluid reasoning [56], task-switching [43], mathematical skills [57], reading comprehension [58], affect control [59], inhibitory function [58], and impulse control [129].

Inhibitory Control Training Among the various executive processes affected by alcohol, rehabilitation of inhibitory control (IC) deficits may confer particular advantage. IC processes suppress irrelevant information, prepotent responding, and implicit attentional biases, facilitating efficient, intentional control of cognitive and behavioral functions. IC deficits are common in AUD [60] implicated in the neurobehavioral sequelae of alcoholism [61] and increase relapse vulnerability [62]. Thus, IC constitutes a candidate mechanism through which neurocognitive recovery may mediate treatment outcomes, and a promising target for intervention. However, few CT studies selectively target IC. The available work largely focuses on neurophysiological outcomes of IC training. This work illustrates the plasticity of prefrontal IC networks in response to training [63], and commonly notes training-associated increases in neural efficiency, including training-associated increases prefrontal activation in anticipation of inhibited behaviors [64] and decreased activation during active inhibition, with no concurrent performance decrements [65]. Training-associated improvements in efficiency appear closely related to gains in training performance [66]. Taken together, this work supports the hypothesis that IC training can benefit cognitive and functional outcomes in AUD. The strength of this support is limited by the paucity of studies evaluating transfer and methodological shortcomings in the available work, including failures to limit stimulus-response (S-R) learning during training, exceptionally short training durations, and use of non-adaptive training tasks. Thus, the current IC training task is necessarily novel, but is informed by contemporary CT methodologies.

Cognitive Training Methodologies Heterogeneity in methods and samples across the CT literature challenge selection of a single, optimal, training approach for AUD, but provide substantial methodological guidance. **Training Performance & Difficulty** Transfer is closely associated with performance during training (e.g., [59,67]). Although transfer is limited to training conditions that tax cognitive resources, the relationships between difficulty, training performance, and transfer are complex. Training performance is negatively associated with subjective ratings of task “difficulty” and “effortfulness”, but positively associated with ratings of “challenging” and “not overwhelming” [67]. Training optimization appears to depend on appropriate titration of task demands to cognitive capacity. Thus, training tasks must be capable of dynamically adapting difficulty to match individual performance. **Duration** Variance in training frequency, magnitude, and duration persists across the literature. Common session lengths range from 25 minutes (e.g., [56]) to 1 hour (e.g., [68]). Total training across sessions ranges from 6 hours (e.g., [69,70]) to 40+ (e.g., [71,72]). A particular challenge to the employment of CT as an adjunct to AUD treatment involves practical considerations of delivery within typical treatment durations (~30 days). Critically, training magnitudes of 10-14 hours are common, and demonstrate transfer across diverse samples (e.g., [43,73,74]), including those with use disorders [54,75]. Dose-response analyses suggest transfer effects are unlikely to asymptote within this 10-14 hour range, with one study noting greater transfer in the latter of two 10-session training blocks [76]. Thus, findings suggest the utility of interventions administered within typical treatment durations, as well as those extending past treatment discharge, providing potential future extension of the current work. **Motivation** Training performance and subsequent transfer are enhanced by participant motivation, although relationships appear limited to intrinsic factors. Extrinsic (i.e., monetary) motivation appears to shift behavioral goals from task performance to task completion; compensation magnitude is negatively associated with training performance, transfer effect sizes, and subjective ratings of task engagement (e.g., [77]). While motivation-directed modifications can improve engagement, performance, and transfer [78], negative findings caution against potential distraction or frustration (e.g., persistent onscreen display of score [79]). **Sensory Modality** Multi-modal tasks recruit additional neural systems, promote multisensory integration, and require executive control processes to shift attention and direct behavioral responding between modalities. Thus, dual-modality training designs are common. Jaeggi and colleagues [56] adapted an *n*-back WM task to include visuo-spatial and auditory components. This “dual *n*-back” task is now widely employed. Modifications by Schweizer et al. [59] provide the basis for WM training in this project. **Control** Appropriately controlling for CT is challenging.

The literature includes 1) no control group; 2) “no-contact” or “treatment as usual” controls completing only pre/post assessments; 3) control for computer usage only, 4) active controls (e.g., computerized trivia [80]); 5) “low difficulty” active controls with non-taxing versions of the training; 6) and “adaptive difficulty” active controls using alternate tasks with putatively low efficacy to induce transfer (e.g., [81]).

Cognitive Training & Alcohol A growing literature indicates CT is associated improvements in executive functions and impulse control in individuals with substance use disorders [e.g., 129,130] However, excepting bias modification training (discussed below), few CT studies focus on alcohol. Rupp and colleagues [75] demonstrated improvements in attention and memory performance among treatment-seeking individuals with AUD and “mild” (>1 SD from norms) cognitive deficits. They administered up to 62 training tasks (final number unspecified) over 12 sessions (45-60 min). Training task selection was individualized, informed by specific impairment. Training was associated with reduced compulsion for alcohol, but drinking outcomes were not evaluated. In an AUD sample, Snider and colleagues report proximal transfer following WM training, as well as rate-dependent improvements in delay discounting and episodic future thinking [131]. Gamito et al. [82] administered 10 sessions (60 min) to inpatient treatment-seeking alcoholics using twelve training tasks. Improvements in executive functions were observed, but training effects on post-discharge outcomes were not evaluated. Both studies employed no contact controls. Houben and colleagues [83] investigated WM training in problem drinkers (AUDIT scores ≥ 8). Three WM tasks were applied over the ~30 day training period (session lengths unspecified). The experimental group reduced drinking by ~10 drinks/week over training and at one-month follow-up. Drinking outcomes were mediated by training performance. No reduction was observed in active controls. These investigations provide critical demonstration of feasibility in AUD, but fail to examine relationships between cognitive transfer and functional outcomes. Moreover, their employment of multiple training tasks and/or lack of targeted cognitive processes (excepting Houben et al. [83]) limits their capacity to inform future intervention development. Empirical study of single-task, process-oriented training will provide the necessary framework to facilitate optimization of complex multi-task approaches.

Bias Modification Cognitive biases for alcohol include the implicit direction of attention toward alcohol cues and the facilitation of alcohol-associated approach behaviors. These biases contribute to loss of behavioral control in AUD (for review see [84]), and are targeted by bias modification (BM) interventions. BM approaches weaken stimulus-response (S-R) associations and reactivity to alcohol cues [85,86], and can improve treatment outcomes [87]. Wiers and colleagues developed the alcohol Approach-Avoidance Task (AAT), a BM method utilizing repeated sessions of directed avoidance responses to alcohol cues [88]. AAT training evinces marked reductions in one-year relapse rates [89], which have been replicated in large samples [90,128]. The efficacy of BM, taken together with the *lack of observed or hypothesized improvement in cognitive gains*, suggests a unique opportunity; adaptive BM paradigms can provide appropriate active control for neurocognitive outcomes, confer potential benefit to participants, and provide a mechanistically-distinct positive control for drinking outcomes.

5. Aims

(H=hypothesis, E=empirical question)

AIM 1: Determine Degree of Cognitive Gains (Transfer) in Response to Training.

Consistent with the extant training and alcohol literatures, we predict that applied as a treatment adjunct, and compared to BM and NTC controls, **H1:** WM and IC training will evince proximal transfer of cognitive gains. **H2:** WM training will evince distal transfer of gains in IC and other executive functions.

In the absence of a consistent literature, we ask, **E1**: Will IC training evince distal transfer, either to WM or other executive functions? **E2**: Will the degree of transfer be equivalent between interventions? **E3**: Will individual differences (e.g., sex; education; AUD severity) impact the strength of these relationships?

AIM 2: Identify Factors Predicting Training Efficacy.

Guided by a substantial CT literature, but lacking evidence specific to AUD samples, we hypothesize models wherein **H3**: Greater performance improvement across training will increase the magnitude of cognitive transfer following WM and IC (but not BM) interventions. Within this framework, we suggest **H4**: Training-related engagement, self-efficacy, and motivation will enhance training performance in all groups, but will be associated with cognitive transfer only in WM and IC groups. We will repeat **E3**, interrogating the potential import of relevant covariates to training efficacy, and comparing those relationships between interventions.

Exploratory Aim: Evaluate and Compare Post-Discharge Functional Outcomes of Cognitive Training.

No investigation of CT applied during AUD treatment has evaluated post-discharge drinking outcomes. Thus, this aim is necessarily exploratory. Based on related work, we hypothesize **H5**: post-discharge alcohol consumption/craving will be reduced in WM, IC, and BM groups relative to NTCs, but will be equivalent between these active groups. **H6**: Cognitive transfer in WM/IC groups (Aim 1) will predict post-discharge consumption/craving outcomes. We ask, **E4**: Will IC or WM training improve post-discharge measures of intra/interpersonal function, relative to controls?

6. Research Plan

The fundamental approach is a repeated measures [Baseline vs. Post-training] design with three intervention arms [Training Conditions: Working Memory Training (WM); Inhibitory Control Training (IC); Bias Modification Training (BM)] and one non-trained control [NTC] group. Intervention assignment will be randomized within sex ($N=120$; $n=30$ /condition; 141 Ss enrolled, consistent with estimated ~15% dropout following initiation of training; power analysis included below). Blocked randomization (block size 3) will be employed. NTC assignment will be non-random; given difference in task demands and resulting compensation, NTC inclusion will be conducted without overlapping the inclusion periods for active interventions, thus avoiding potential interpersonal conflict. The schedule (Table 1) facilitates application of screening (Table 2), baseline/post-training assessment (Tables 3/4), and 12 training sessions (30-40 min each) within typical inpatient stay following medical detoxification. Functional outcomes are assessed via follow-up interviews conducted 2, 4, and 6 weeks (+/- 7 days), post-discharge.

Table 1	Treatment Day (Post-detox)														Weeks (Post-discharge)					
	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	2	3	4	5	6
Study Phase																				
Screening																				
Baseline																				
Training																				
Post-Assess																				
Follow-up																				

Development of the overall approach, including screening, training/transfer tasks, and follow-up interviews was informed by our past (e.g., [91,92]) and current [93] research in treatment-seeking AUD populations. Screening measures include questionnaires developed by, and utilized in, the Neurocognitive Laboratory (Sara Jo Nixon, Director) and employed in current studies/protocols.

Table 2	Measure/Instrument	Abbrev.	Refs
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Mood	Spielberger Anxiety Inventory	AI	[94]
	Beck Depression Inventory-II	BDI-II	[95]
Substance Use	Alcohol Use Questionnaire	AUQ	[96]
	Substance Use History	SUH	[91]
	Drugs of Choice Questionnaire	DOC	[91]
	Family History	FH	[98]
	Short Inventory of Problems-Alc	SIP-2RA	[99]
	Short Inventory of Problems-Drug	SIP-2RD	[99]
Physical / Mental Health & Function	Past Experiences	PC-PTSD	[139]
	Difficulties with Emotion Regulation	DERS	[135]
	Impulsivity Assessment	S-UPPS-P	[134]
	Interpersonal Problem Inventory	IIP-32	[133]
	Pain Questionnaire	PQ	[141]
Diagnostic	Structured Clinical Interview DSM-5	SCID-5RV	[100]

Participant Screening

Consistent with ongoing work, subjects (Ss) are recruited from residential substance abuse treatment facilities in North Central Florida. Facility access has been granted through longstanding collaborative relationships with treatment facilities. Screening is conducted within treatment facilities. Ss will have completed medical detox (if required). To afford comparison with

current/previous studies and limit potential confounds of age and education in cognitive performance, Ss will range in age from 25-64, with at least 10 years of education. In addition to providing basic demographic and health information, Ss complete questionnaires querying affect, personal/familial substance use, consequences of use, and physical/mental health & functioning (Table 2). Suicidal intent is not queried (the Beck Depression Inventory [BDI-II] will include modified versions with no reference to suicidal ideation), but incidental communication of intent to harm self or others will be immediately reported to facility clinical staff. *Time: ~60min; Compensation: \$20*

Table 3	Outcome Measure/Task	Abbrev.	Refs
General Executive	Trail-Making Test - A/B	TMT-A/B	[101]
	Digit Symbol Substitution	DSST	[102]
	Raven's Matrices-Abbrev.	RPM-9	[103]
Working Memory	Sternberg Short-term Mem.	Sternberg	[105]
	Visuospatial WM	Corsi	[137]
	n-back WM task	n-back	[108]
Inhibitory Control & Impulsivity	Emotional Stroop	StroopEmo	[110]
	Stroop Color-Word	StroopCW	[111]
	Reward Discounting-Abbrev.	DRD-8	[112]

Baseline & Post-Training Assessment

Assessments are conducted in private rooms within the treatment facilities. To promote comparison with related investigations, assessment battery selection was informed by alcohol-related cognitive recovery literature, the cognitive training literature, and our current work. Three groups of assessment tasks are employed to interrogate executive functioning, including 'general executive' assessments (e.g., set-shifting, abstraction), and those specific to working memory and inhibitory control (Table 3). To reduce subject burden and facilitate timely assessment, task durations are relatively short (≤ 5 min), with tasks including either brief well-established neuropsychological measures (e.g., Trail-Making Test Forms A/B; [101]) or well-validated abbreviated versions (e.g., 9-item Raven's Matrices; [103]). To limit sequence effects, pseudorandom task ordering will be employed, with no two tasks in the same domain following sequentially. Task order will be maintained between baseline and post-training assessments. Alternate forms of the tasks are employed to limit practice effects. Additionally, several measures assessing functional changes (e.g., self-efficacy,

Table 4	Measure/Instrument	Abbrev.	Refs
Functional Change Measures	Alcohol Self-Efficacy	AASE-B	[138]
	Spielberger Anxiety Inventory	AI	[94]
	Beck Depression Inventory-II	BDI-II	[95]
	Alexithymia Scale	TAS-20	[132]
	General Self-Efficacy	GSE	[140]
	Readiness to Change	RCQ-TV	[136]
	Difficult with Emotion Regulation	DERS	[135]
	MACE	MACE	[120]
	Pain Questionnaire	PQ	[141]
Attn. Bias	Implicit Association Test	Alc-IAT	[114]

readiness to change) will be ascertained (Table 4). If screening and baseline materials are administered during a single visit, shared measures will be assessed only once (e.g., BDI-II).

Time: ~90 min; Compensation: \$20

Training

For all trained groups, up to twelve training sessions will be conducted over no more than three weeks, with each lasting approximately 30-40 min. Training will be administered via tablet computer, utilizing a self-guided

user interface. Prospective discharge dates are reviewed at screening to insure feasibility of training completion. Ss will be discontinued if they complete fewer than 3 sessions in the first week, or if comparison of training progression and prospective discharge dates indicate completion of fewer than 8 sessions will be possible. Assessments will be conducted at least one day after the last training session. **Performance-based Compensation** To limit attrition, enhance compliance, and avoid potential confounds of extrinsic compensation [77], we utilize performance-based compensation *which will maintain equal payment across all subjects*. The training tasks continuously titrate difficulty to match performance capacity, thus within a training session the occurrence of within-session performance improvements is common, and will result in performance-based compensation 3 ± 1 times/session (\$5 increments; Total payment for all subjects completing all twelve sessions = \$180).

Working Memory Training The dual n-back task involves simultaneous presentation of visual and auditory stimuli, and is well-characterized in CT. Our ongoing work employs a dual n-back task developed by Schweizer and colleagues (2011), which was modified for use in the current project. Visual stimuli are presented on a 4 x 4 grid of white tiles. In each trial, one tile is darkened (Fig. 1). Auditory stimuli are presented via headset and include letters or single-digit numbers. Using a 2-button response pad, subjects indicate whether the position of the darkened tile OR the auditory stimuli match those of the trial presented “*n*-back”. Each trial lasts 3000ms, including simultaneous stimulus presentation (500ms) and ITI (2500ms). The ITI includes a 2000ms response window, during which Ss respond via key-press if either stimuli corresponded to those presented *n* trials back (left/right buttons for visual/auditory stimuli, respectively). Auditory feedback (250ms) is played immediately after a correct (chime) or incorrect (low tone) button-press, or at 2000ms in target trials with response omissions (buzz). A standard block is 20+*n* trials, including 8 single-modality target trials (4 visual/4 auditory), 2 dual-modality target trials, and *n*+10 non-target trials. $\geq 70\%$ accuracy increases *n*-level by 1 in the subsequent block. $\leq 50\%$ accuracy results in decreased difficulty.

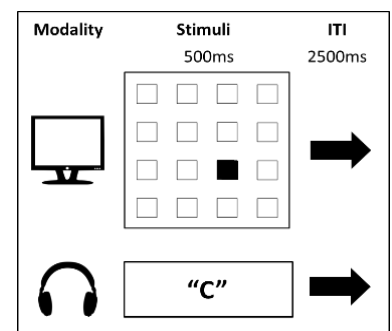


Fig 1. WM Training Modified from Jaeggi [56] and Schweizer [59]

Go/NoGo Training Task: Ss are instructed to respond as quickly and accurately as possible to cues designated as “Go” stimuli by pressing a response button with the dominant index finger, and to withhold responding to “NoGo” stimuli. To maintain the prepotency of Go responses, each block will include 60 Go and 30 NoGo stimuli. Visual stimuli include combinations of four basic shapes (circle/square/triangle/diamond) and colors (blue/yellow/orange/purple). Auditory stimuli include spoken letters or single-digit numbers (e.g., “Six”), and are presented simultaneously with visual stimuli. For each block, instructions will designate one modality as “dominant”, and one “subordinate”, directing appropriate responding when rules conflict. To preclude strategy-based inattention (e.g., closed eyes) to the subordinate modality, stimuli from the dominant modality will be absent in 30 trials. Thus, each block will include 60 Go trials (20 corresponding; 20 conflicting; 20 subordinate cues only) and 30 NoGo trials (10 corresponding; 10 conflicting; 10 subordinate cues only). Instructional sets are varied for each block, precluding significant S-R contribution to performance. Each trial includes presentation of a fixation cross varying in duration from 1500-1900ms, followed by stimulus presentation (500ms) and a variable response window. Following instruction presentation, Ss complete 9 practice trials (6 Go/3 NoGo). Subject reaction times (RTs) during practice trials are used to establish response window thresholds for subsequent task performance [65], facilitating titration of difficulty to individual performance. Ss remain naïve to the calibration procedure.

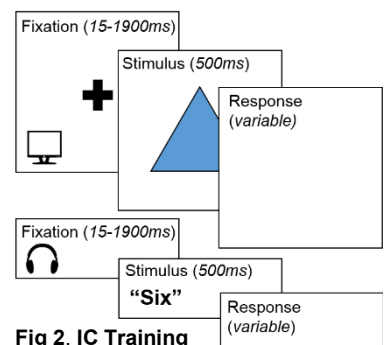


Fig 2. IC Training

Auditory feedback (250ms) is played immediately after correct (chime) or incorrect (low tone) button-press, or at cessation of response window (buzz) to signal late responding/incorrect omission. A typical training trial is depicted in Fig. 2.

Bias Modification Training The BM group will train using an alcohol-specific, dual-modality, approach-avoidance task, modified from Wiers and colleagues [88]. Responses on this task result in rapid reduction or enlargement of the visual stimuli (i.e., “zooming out/in”), consistent with “pushing” stimuli away or “pulling” them closer. Two instructional conditions are employed throughout training. In the ‘explicit’ condition, Ss are instructed to “push” in response to alcohol-related visual stimuli. In the ‘implicit’ condition, Ss are instructed to respond to visual stimuli based on accompanying auditory or visual discriminatory features (e.g., chime vs. low tone; landscape vs. portrait orientation). All alcohol-related stimuli presented in the implicit condition are paired with discriminatory characteristics eliciting pushes. To control for the progressive difficulty utilized in experimental training, response time thresholds will vary based on individual performance, as described in IC training. Discrimination difficulty will also increase progressively (e.g., square vs. circle in early implicit trials; rectangle vs. parallelogram in later trials).

Follow-up Interviews Ss will be contacted by phone at 2, 4, and 6 weeks (+/- 7 days), post-discharge. The Project MATCH modification of the timeline follow-back (TLFB; [119]) will assess quantity and frequency of daily substance use. The Mini Alcohol Craving Experience (MACE) questionnaire will provide a brief, psychometrically robust measure of craving [120]. Interpersonal function and social support will be assessed with Moos’ Health and Daily Living Scales (Part VI: “Your friends and family” [121]). Mood will be queried with the modified Beck Depression Inventory (BDI-II; [95]) and Anxiety Index (AI; [94]). *Time: ≤30 min/each; Compensation: \$20/each*

Analysis **Aim 1:** Initial transfer analyses will be conducted using repeated measures multivariate GLM (MANOVA). Three combinations of dependent variables (DVs) will be analyzed according to their putative cognitive domains: Working Memory, Inhibitory Control, and General Executive Functions. Based on the substantial heterogeneity in short-term recovery trajectories [31], this approach was selected in lieu of covarying for baseline scores, to avoid inappropriate assumption of homogeneity of regression slopes. As dictated by preliminary data analysis, MANOVA may be expanded to include potentially important covariates (e.g., MANCOVA with sex, education, AUD severity). If initial analyses of composite scores fail to support hypotheses regarding transfer effects, factorial GLM will be applied to individual DVs, with conservative correction for Type 1 error. **Aim 2:** Linear contrasts will characterize between-group differences in performance across training sessions. Training performance metrics include mean difficulty level, accuracy, RT, and efficiency (speed/accuracy tradeoffs). Repeated measures generalized linear mixed models (GLMM) will characterize relationships between training-related measures and cognitive gains. Fixed effects will include intervention arm, training performance slopes, and their interaction. Random effects will include parameters modeling variation between subjects (e.g., age), as appropriate. Analyses of data missing not at random (MNAR) will be conducted. MNAR data will be handled in consultation with statistical collaborators. Latent growth curve models will be developed to characterize relationships between individual differences (e.g., age, education), training-related factors (i.e., training/frequency), and cognitive gains. **Exploratory Aim:** GLMM analysis strategy described in Aim 2 will be extended to include functional outcomes. Fixed effects will initially include group, time, and their interaction. Secondary analyses will incorporate training performance, number of sessions completed, and relevant covariates, as appropriate. Time-to-relapse analyses will be conducted using discrete-time models. **Power** CT meta-analyses commonly report effect

sizes (ESs) in the medium-to-large range (e.g., [123,124]). In a dual n-back training paradigm highly similar to the current intervention, Schweizer [59] reported ESs of .10 and .16 (partial eta squared; $p\text{-}\eta^2$) for group by time interactions and between-group effects, respectively. In an AUD sample, Rupp [75] observed ESs of .10-.12 ($p\text{-}\eta^2$) using DVs identical or highly similar to those utilized in the current project. Using a WM CT approach, Houben [83] observed an ES of .16 ($p\text{-}\eta^2$) for reduced alcohol consumption. In a BM RCT, Eberl [90] observed a .09 ES ($p\text{-}\eta^2$) for relapse reduction. Based on these reports, an estimated $p\text{-}\eta^2$ value of .10 (Cohen's $f=.33$) was applied to power analyses, conducted with G*Power (v3.1.9.2). Power estimates for Aims 1 and 2 used $\rho=.81$, calculated from averaged correlations between neurocognitive measures taken ~30 days apart in a sample of recently-detoxified AUD individuals [127]. Calculations included $n=120$ and $\alpha=.05$. MANOVA estimates indicated power to detect between group effects and between-within interactions at .89 and .86, respectively. A GLM design was used to estimate power for GLMM analyses. Between and between-within power estimates were .90 and .99 for Aim 2 analyses, respectively. Power estimates for analysis of functional outcomes used $\rho=.5$, $n=102$ (accounting for ~15% post discharge attrition), and $\alpha=.05$. Estimates for between group effects and between-within interactions were .93 and .99, respectively. This analysis assumes no missing data for participants retained, and is thus likely an overestimate. Given challenges associated with tracking this highly-mobile sample, analysis of required sample size to maintain .80 power was conducted, revealing power would remain robust to loss of up to 40% of the full sample to attrition or incomplete follow-up data.

7. Possible Discomforts and Risks

Human Subjects Involvement, Characteristics, and Design Subjects (Ss) with alcohol use disorders (AUDs) will be recruited from inpatient substance abuse treatment facilities in North Central Florida. Our group has maintained long collaborative relationships with these facilities, which provide private space to conduct screening & research procedures. Ss will have completed any medical detoxification prior to screening. Following provision of written, informed consent, Ss complete detailed questionnaires querying demographic information, general health, medical history, affect, and personal/familial substance use. Ss continuing to meet selection criteria then complete a brief diagnostic interview (Structured Clinical Interview for DSM-5, Research Version [SCID-5RV]).

Selection Criteria Ss will be between 25-64 years of age, with a minimum of 10 years of education. Ss will meet DSM-5 criteria for at least moderate AUD. Recruitment will be limited to Ss reporting alcohol problem chronicity of ≥ 5 years; previous work indicates reports of ≤ 5 years are uncommon in this population. Our prior work indicates that exclusion for anti-social personality disorder, past trauma, generalized anxiety disorders, or major depressive disorder would limit generalizability of results and compromise recruitment. Thus, measures are included to characterize associated traits/symptomatology, facilitating descriptive or covariate analyses. Ss will be excluded if self-reported symptomatology suggests probabilistic diagnoses for any psychotic disorder, current/unremitted panic disorder, or bipolar disorder. Following screening, subjects are informed if they meet selection criteria. To avoid biasing future selection efforts, selection criteria are not revealed to subjects. Consistent with IRB guidance, details regarding subject exclusion are not discussed with clinical staff, with the exceptions of suicidal ideation or intent to harm self/others.

Endorsement of suicidal intent through incidental communication will result in immediate contact with clinical staff. As communicated during informed consent and in ICFs, only suicidal intent or intent to injure self/others will constitute exceptions to participant confidentiality. Neither are queried, and would be revealed only through incidental communication.

Inclusion Criteria

- Ss 25-64 years old
- Minimum of 10 years of education
- Meet DSM-5 criteria for at least moderate AUD
- Alcohol problem chronicity of ≥ 5 years

Exclusion Criteria

- Medical histories confounding interpretation regarding change in neuropsychological functioning (e.g. stroke)
- Meet DSM-5 criteria for current/unremitted psychotic, panic, or bipolar disorders as determined by Structured Clinical Interview for DSM-5, Research Version [SCID-5RV]

Based on current work, we expect to recruit a sample consisting of approximately 69% Caucasian, 28% African American, and 3% “other” or multiple races. We anticipate 7% of the sample will endorse Hispanic ethnicity. Recruitment, compliance, and retention efforts will be supported by financial compensation. Total possible compensation for trained groups, including screening (\$20), baseline/post-training assessments (\$40 total), completion of 12 training sessions (\$180 total), a bonus for each training completed (\$60 total), and 3 follow-up interviews (\$60 total), is \$360. Total possible compensation for non-trained controls is \$120. Retention will be enhanced by subject tracking procedures utilized in ongoing projects, including the maintenance of detailed primary and secondary contact information and alternate contact information. Research staff are trained in the use of secondary/alternate contacts to re-establish communication with participants without compromising confidentiality.

Participants are randomly assigned to one of the three active intervention arms (2 experimental; 1 active control), or a non-treated control group. The nature of cognitive training interventions precludes blinding procedures. The use of computerized assessment tasks (i.e., lack of human scoring vulnerable to potential bias) and participant self-report data limits risks associated with bias in non-blinded procedures.

Sources of Materials Ss complete paper/pencil questionnaires, computerized cognitive assessment batteries, computerized cognitive training tasks, and phone follow-up interviews. Data collected during screening include probabilistic psychiatric diagnoses and self-reported demographic information, general health, medical history, affect, and personal/familial substance use histories. Data collected during training tasks includes behavioral performance data (e.g., reaction times); no personal identifiers or dates are included. Tablet PCs have all internet

access/functionality removed, excepting whitelisted cloud servers for data transfer/storage. Baseline/post-training assessments collect behavioral performance data as well as self-reported measures of function (e.g., self-efficacy, mood). Follow-up interviews collect self-reports of substance use, alcohol craving, affect, quality of life, and social support. None of these protocols involve invasive techniques. *No biospecimens are collected. Medical records are not accessed.* Participant data will be assigned alphanumeric codes containing no personal identifiers, and are scored, filed, and retained in a manner designed to facilitate confidentiality. Alphanumeric codes do not appear on ICFs, which are stored in separate, locked containers. The file linking subject names with alphanumeric codes is password-protected and retained on an encrypted University of Florida network. Only staff completing HIPAA, local IRB and NIH training in human research will have access to individually identifiable subject information. Electronic data will be stored and maintained using REDCap (Research Electronic Data Capture, Vanderbilt University), with protected health information de-identified.

Potential Risks The primary risk is a violation of confidentiality. Disclosure of medical, substance use, and other personal information could pose psychological, financial, or legal risks to subjects. Although these risks are potentially serious, their likelihood is mitigated by the extensive precautions described above, including physical and electronic security measures, use of alphanumeric codes, removal of identifiers, and ongoing training in responsible conduct of human subjects research. This low likelihood is reflected by the absence of any breach in confidentiality in our past or current projects. A second risk involves potential psychological discomfort in responding to interview questions/questionnaires, which query potentially personal or sensitive information. Research staff are trained regarding sensitivity to these issues, and will remind participants of both the confidential nature of the collected information and opportunity to skip questions they are not comfortable responding to. In our past and ongoing work, no incidents related to subject discomfort in disclosing sensitive information have occurred. A third risk involves potential fatigue associated with assessment and training tasks. To limit this risk, assessments are limited to approximately 90 minutes, and training sessions to approximately 30-40 minutes. Both include scheduled rest breaks.

The proposed interventions are novel. There is no current “standard of care” for neurocognitive rehabilitation in AUD. Thus, standardized alternative interventions are unavailable.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent Ss are recruited from substance abuse treatment facilities through in-person announcements by trained research staff. Potential Ss indicate interest directly to research staff. The study is further described to interested individuals, and contingent on their continued interest, the informed consent process is initiated. Ss are specifically informed of risks and protections against risks. Ss are informed that participation will not impact their clinical care. Confidentiality is emphasized, as are explicit exceptions to confidentiality (i.e., suicidal intent, intent to harm self/others). No deception is utilized in describing study aims or procedures. Ss are informed

of the random assignment to intervention groups. Ss may retain a full description of the study, enabling them to review it with friends/family/peers/counselors prior to providing consent. Research staff will be trained in informed consent procedures through local IRB, NIH, and PI-directed training. All procedures and consent forms will be approved by the University of Florida Health Science Center Institutional Review Board.

Protections Against Risk To protect privacy, individuals complete screening materials in an area separate from clinical activities and without the presence of clinical staff. Materials are completed with the instruction and aid of trained research staff. The diagnostic interview, baseline/post-intervention assessments, and training sessions are conducted in private rooms at the treatment facilities.

As described above, all data will be coded alphanumerically, with no personal identifiers attached. Data are scored, filed, and retained in a manner designed to facilitate confidentiality. Alphanumeric codes do not appear on ICFs, which are stored in separate, locked containers. To confer further protection against risks, ICFs are specifically designed to include no references to alcohol use disorders or treatment. The file linking subject names with alphanumeric codes is password-protected and retained on an encrypted University of Florida network. All data collected via tablet computers include only behavioral training performance data. No personal identifiers or dates are included. Tablet PCs have all internet access/functionality removed, excepting whitelisted cloud servers for data transfer/storage. Only staff completing HIPAA, local IRB and NIH training in human research will have access to individually identifiable subject information. Ss will be further protected by an NIH certificate of confidentiality. Subjects may withdraw at any point in screening, testing, or training without impacting their clinical care. Adverse events are documented and reported as described in the data safety and monitoring plan (DSMP), below.

8. Possible Benefits

Although cognitive training interventions have demonstrated some benefits, and participants may display benefits during and following training, it is not clear that these benefits apply to untrained tasks or impact daily function during or following treatment. The project's examination of these potential benefits may inform future recovery interventions for alcohol use disorder, providing potential value to individuals with AUD and society.

9. Conflict of Interest

No conflict of interest is declared.

DATA AND SAFETY MONITORING PLAN

The current project involves no acute administration of any substance. The project involves initial screening, neurocognitive testing and repeated cognitive training using computerized tasks at inpatient treatment facilities. This study is not a Phase III trial, multi-site trial, or high-risk intervention, thus no

Data Safety Monitoring Board will be utilized.

Reporting and Monitoring of Adverse Events The PI, informed by NIH, FDA, and local IRB guidelines, will be responsible for distinguishing serious adverse events (SAEs), from non-serious adverse events (AEs) and unanticipated problems. Every SAE and unanticipated problem 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 the nature of this project, which involves training with computerized cognitive tasks, and the rigorous safety precautions employed by our laboratory, severe adverse events are not anticipated. All events or unanticipated problems will be reviewed at weekly staff meetings. Should a pattern of adverse events be detected, the protocol will be re-evaluated and amended, as appropriate. Follow-up reports for all SAEs and unanticipated problems will be conducted. Timing and content of these reports will be dictated the nature of the event. Initial and follow-up reports to the NIAAA project officer will be conducted and submitted using the forms/guidelines outlined in the COMBINE Monograph Series (DHHS Publication No. 04-5289).

Subjects will be contacted by phone at 2, 4 and 6 weeks (+/- 7 days) following discharge from treatment. The Project MATCH modification of the timeline follow-back (TLFB) will be used to assess the quantity and frequency of daily substance use over the period since last contact with study staff. Subjects will be informed of NIAAA guidelines for low-risk drinking. If participants report patterns of use exceeding these guidelines, patterns consistent with binge-drinking, or any substance abuse, they will be provided with contact information for local alcohol/substance abuse treatment programs and community support groups. If, during the course of the follow-up interview, subjects communicate serious psychiatric or medical symptoms, relevant referral information and resources will be provided. All events occurring during the course of the phone follow-ups will be handled consistent with methods described above, including report of SAEs and unanticipated problems to the NIAAA project officer and local IRB within 48 hours.

Annual Reports Annual reports summarizing all AEs will be provided to the NIAAA project officer. Reports will include 1) a summary of any data and safety monitoring issues that occurred since the previous reporting period; 2) a description of any changes in the research protocol or data and safety monitoring plan that may affect risk; and 3) all new and continuing IRB approvals.

Data Quality Assurance and Confidentiality The primary risk is a violation of 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 restricted-access University of Florida system. All study personnel will complete IRB and NIH training in human subjects protection and responsible conduct of research. Trained research assistants will hand-enter all data from pencil/paper tasks and questionnaires into REDCap, with protected health information de-identified. To ensure the quality of entered data, all data entry will be subsequently verified by another trained research assistant. Major discrepancies will be noted and discussed at weekly staff meetings. NIH Certificate of Confidentiality will enhance protection of data obtained throughout the project.

Pregnancy Testing Participation in the study involves only paper/pencil questionnaires, interviews, and computerized tasks. These activities pose no specific risks to pregnant women or fetuses. Thus, pregnancy will not be included as a selection criteria and pregnancy testing will not be conducted.

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