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Frontal tDCS reduces alcohol relapse rates by increasing connections from left dorsolateral prefrontal cortex to addiction networks

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ABSTRACT

Background: Brain-based interventions are needed to address persistent relapse in alcohol use disorder (AUD). Neuroimaging evidence suggests higher frontal connectivity as well as higher within-network connectivity of theoretically defined addiction networks are associated with reduced relapse rates and extended abstinence during follow-up periods.

Objective: /Hypothesis: A longitudinal randomized double-blind sham-controlled clinical trial investigated whether a non-invasive neuromodulation intervention delivered during early abstinence can (i) modulate connectivity of addiction networks supporting abstinence and (ii) improve relapse rates. Hypotheses: Active transcranial direct current stimulation (tDCS) will (i) increase connectivity of addiction networks known to support abstinence and (ii) reduce relapse rates.

Methods: Short-term abstinent AUD participants (n = 60) were assigned to 5 days of either active tDCS or sham during cognitive training. Causal discovery analysis (CDA) examined the directional influence from left dorsolateral prefrontal cortex (LDLPFC, stimulation site) to addiction networks that support abstinence.

Results: Active tDCS had an effect on the average strength of CDA-determined connectivity from LDLPFC to the incentive salience and negative emotionality addiction networks - increasing in the active tDCS group only. Active tDCS had an effect on relapse rates following the intervention, with lower probability of relapse in the active tDCS vs. sham. Active tDCS showed an unexpected sex-dependent effect on relapse rates.

Conclusion: Our results suggest that LDLPFC stimulation delivered during early abstinence has an effect on addiction networks supporting abstinence and on relapse rates. The unexpected sex-dependent neuromodulation effects need to be further examined in larger clinical trials.

1. Introduction

Alcohol use disorder (AUD) continues to directly afflict about 24 million individuals and impact the lives of many millions more. The low success rate of current psychosocially-based (e.g. 12-step) treatment programs (~64% relapse within a year) highlights the need for new and effective interventions that target underlying biological factors contributing to relapse. Non-invasive neuromodulation interventions continue to provide promising results in AUD [1–3].

Neuroimaging research has identified targets for *brain-based* non-invasive interventions. Our past resting-state fMRI studies contributed to this literature by reporting that connectivity of left dorsolateral prefrontal cortex (LDLPFC) and nucleus accumbens during early abstinence is associated with future treatment outcome with: (a) higher LDLPFC-accumbens connectivity in long-vs. short-term abstinence or controls [4,5]; (b) lower [6] and decreasing [7,8] LDLPFC-accumbens connectivity during early abstinence as a predictor of subsequent relapse. Moving beyond the examination of region to region connectivity, we examined resting state functional connectivity within theoretically defined addiction networks [9]: the incentive salience (IS), negative

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emotionality (NE), executive functioning Go (EF/Go), and executive functioning Stop (EF/Stop) networks [10,11]. We reported that the connectivity strength within each of these theoretically defined addiction networks measured during early abstinence was associated with subsequent relapse outcomes, while connectivity within a sensory processing -primary visual-network was not [9]. The addiction network that showed the strongest effect was the IS: higher within-network connectivity in IS during early abstinence decreased the odds of relapse in the subsequent month [9].

The above neuroimaging data indicates that early abstinence is a critical period during which enhanced connectivity of frontal and addiction networks serves as a protective factor to support subsequent abstinence. Based on this evidence, non-invasive neuromodulation interventions that support abstinence maintenance need to be designed to increase frontal and addiction network connections and delivered during critically vulnerable stages of recovery such as early abstinence.

Effect of DLPFC stimulation on treatment outcome in substance use disorder. Preclinical [12,13] and clinical [2,3,14] studies suggest DLPFC stimulation is a promising intervention target for neuromodulation trials in substance use disorder. While most studies report reduced AUD symptomatology following tDCS intervention [1], inconsistent findings still remain. For example, there are reports of (a) no additive tDCS effects of tDCS on self-reported craving after mindfulness-based relapse prevention therapy [15] and (b) no tDCS effects on the amount of alcohol consumption in risk-drinkers undergoing cognitive bias modification [16]. Inconsistent findings could be related to infrequent spacing of intervention sessions [15], studying an at-risk population rather than individuals with chronic alcohol use with diagnosed AUD [16], or administering tDCS with concurrent tasks not designed to enhance executive functioning [15,16]. The present study administered five consecutive days of DLPFC stimulation sessions on short-term abstinent individuals diagnosed with AUD using a combination of tDCS and concurrent cognitive training.

Effect of DLPFC stimulation on connectivity. Growing evidence from studies combining non-invasive neuromodulation and neuroimaging techniques report increases in connectivity following DLPFC stimulation [17–22]. For example, a study on abstinent individuals with methamphetamine use disorder, reported that connectivity within the executive functioning and incentive salience networks increased following one tDCS session targeting DLPFC [23]. Another study on individuals with AUD reported an increase in global efficiency and a significant reduction in global clustering following five tDCS sessions targeting DLPFC [2]. The current study adds to the literature by (i) examining the effect of DLPFC stimulation on specific theoretically defined addiction networks [9–11], and (ii) investigating the directional influence of DLPFC stimulation on theoretically defined addiction networks known to support abstinence.

From resting state functional connectivity (RSFC) to resting state causal connectivity. Our past studies have identified RSFC-based markers of abstinence and relapse. RSFC, however, is limited because it lacks information on the directionality of identified significant correlations. The present study sought to go beyond the non-directional correlations of RSFC and conduct analyses that allows us to determine the *causal or directed influence of DLPFC stimulation* on addiction networks known to support abstinence by applying causal discovery analysis (CDA) on our rest fMRI data.

CDA is a powerful data-driven methodology that allows the determination of the directed influence (i.e. the causal connectivity) between variables of interest. A recent large-scale AUD study [24] used CDA to determine the direct causal influence between neural networks, phenotypic domains, and AUD symptom severity. In that study, Rawls et al. (2021) identified a learned causal model in which the strength of a prefrontally mediated executive functioning resting network had the most directional influence on AUD symptom severity. A following paper by the same group [25] focused on using CDA to determine whole-brain causal connectomes from rest fMRI data determining edges or connections between regions and edge orientation [26,27]. The current study used CDA [25] to determine whether the causal connectivity from left dorsolateral prefrontal cortex (LDLPFC below the F3 tDCS anode [28]) to the theoretically defined addiction networks known to support abstinence [9] changes following our neuromodulation intervention.

The present study adds evidence to neuromodulation clinical trials in AUD by: (a) Collecting pre- and post-tDCS resting fMRI data to examine underlying brain connectivity changes, (b) Merging the use of tDCS paired with cognitive training to control participants' effort and engagement during the stimulation session; (c) Using CDA to determine the causal connectivity from the stimulation site (LDLPFC) to previously defined addiction networks known to support abstinence [9,10], and (d) Tracking relapse outcome over a 4-month follow-up period, longer than follow-up periods in previous clinical trials [3,29].

2. Materials and methods

2.1. Participants

A total of 81 participants with AUD were consented (Inclusion/Exclusion criteria in Supplementary Material A). All participants were recruited during early abstinence, 1–2 weeks after being admitted to a 28-day inpatient addiction treatment program in Minneapolis, MN (number of days abstinent until baseline MRI session M = 24.33, SD = 16.47). All participants provided written informed consent and received monetary compensation for participating. The consent process and all procedures were approved by the University of Minnesota Institutional Review Board.

From the 81 participants, 21 did not have complete fMRI (functional magnetic resonance imaging) data because: 10 left the treatment program and were no longer reachable (9 after their pre-intervention neuroimaging session, 1 after the first tDCS session); 4 were found to be no longer eligible (1 because of identified cognitive impairment, 2 because the identified *primary* substance use disorder diagnosis was not alcohol, but stimulant and heroin and 1 because of identified unknown metal in their bodies), 3 voluntarily withdrew participation before the initial tDCS session, 3 were excluded from group analyses because their fMRI data was flagged as having excessive noise (Supplementary Material B, Individual resting state data quality assessment - Motion and

Table 1
Demographics and history of alcohol use in participants who had complete fMRI data.

Characteristic		Intervention Group		
	All AUD (n = 60)	Active tDCS (n = 31)	Sham (n = 29)	Active tDCS vs. Sham
	Mean *or n* (SD *or %*)	Mean *or n* (SD *or %*)	Mean *or n* (SD *or %*)	**T-test or** Chi^2 (italics)
Age	41.65 (9.60)	39.84 (9.97)	43.59 (8.94)	p = 0.13
Years of Education	14.32 (1.98)	14.72 (2.10)	13.89 (1.78)	p = 0.12
Female, n (%)	21 (35.0%)	11 (52.4%)	10 (47.6%)	p = 0.94
Age of AUD onset	28.10 (9.52)	26.80 (7.23)	29.54 (11.52)	p = 0.28
# of standard drinks: Past 6- months	2642.00 (2192.62)	2714.03 (1949.76)	2569.97 (2451.90)	p = 0.823
# of drinking days: Past 6- months	100.11 (61.40)	101.26 (60.48)	98.96 (63.59)	p = 0.898
# of days abstinent until the baseline MRI session	24.33 (16.47)	25.08 (15.93)	23.58 (17.30)	p = 0.756

AUD, Alcohol Use Disorder; MRI, Magnetic Resonance Imaging; SD, Standard Deviation; tDCS, transcranial direct current stimulation. Chi^2, Chi-Square; p, significance probability value.

artifacts), 1 because of scanner hardware issues during scan. As a result, pre- and post-intervention fMRI data was available for 60 participants (Table 1). Timeline Follow-Back (TLFB) [30] recorded alcohol/drug use history for the past 6 months before entering the treatment program (Tables 1 and 2).

2.2. Intervention

Transcranial Direct Current Stimulation (tDCS). tDCS was performed with the StarStim wireless neurostimulator system (Neuroelectrics, Inc., Barcelona, Spain). Direct current was induced by two circular rubber carbon core electrodes in saline-soaked surface sponges (25 cm^2), placed in a neoprene headcap with marked locations based on the 10–20 EEG system [28]. The anodal electrode was at F3 and the cathodal electrode was at F4. Intervention sessions took place twice per day (13 min duration each, separated by 20 min) on five consecutive days [31,32]. For active stimulation, participants received a constant current of 2 mA intensity for 13 min (30 s ramp up/down). For sham stimulation, current was ramped down (30 s) immediately after the initial ramp up period, and then ramped up (30 s) right before the final ramp down portion of the session. Participants completed a questionnaire before and after each tDCS day reporting the presence and severity of potential side effects.[1]

Cognitive task completed during tDCS. Preclinical and clinical literature suggests that chronic substance use is associated with poor cognitive flexibility as measured by the reversal learning set-shifting task [33–36]. We administered the 4-choice reversal learning task [37] (Supplementary Material E) concurrently with each tDCS. Task administration started after the 30 s tDCS ramp up.

2.3. Relapse metrics

All participants were abstinent at the pre- and post-intervention MRI and neuromodulation sessions because these were completed in the addiction treatment program. Participants underwent random alcohol/drug tests in the treatment program. After participants were discharged from the addiction treatment program they completed in-person interviews at the 1- and 4-month follow-up timepoints. Participants were in the relapsing group if they reported consuming at least one drink. Participants who had not consumed any alcohol/drug were considered to be in the abstaining group. One- and 4-month relapse outcomes were defined as separate outcome variables to be able to examine potential durability intervention effects.

Table 2
Counts of lifetime and current substance use disorder for all participants with alcohol use disorder.

Substance	Lifetime Diagnosis Count			Current Diagnoses Count		
	Active tDCS (n = 31)	Sham (n = 29)	Chi^2 Sig.	Active tDCS (n = 31)	Sham (n = 29)	Chi^2 Sig.
Marihuana	12	13	p = 0.58	7	5	p = 0.53
Cocaine	5	4	p = 0.59	0	0	–
Methamphetamine	4	4	p = 0.62	0	0	–
Opioids	1	2	p = 0.51	0	0	–
Hallucinogens	2	4	p = 0.41	0	0	–
Nicotine	17	18	p = 0.67	17	16	p = 0.91

tDCS, transcranial direct current stimulation; Chi^2, Chi-Square; p, significance (Sig.) probability value.

[1] Potential side effects included headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness/fatigue, poor concentration, acute mood change, and nausea. Severity was rated on a scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe).

2.4. Brain imaging metrics

Brain imaging data acquisition, quality assessment, preprocessing and individual level analyses are in Supplementary Material B.

2.5. Group analyses to determine intervention effects

To determine intervention effects on causal connectivity, a 2 (Intervention group: Active tDCS vs. sham) x 2 (Timepoint: pre-vs. post-intervention fMRI) general linear model correcting for baseline was conducted with causal connectivity (standardized r score) between LDLPFC (CDA source) and each addiction network (CDA destinations, Table 3, Supplementary Material C, D) as the dependent variable.

To determine whether causal connectivity changes were different depending on relapse outcome, a 2 (Outcome: Relapsed vs. Abstained) x 2 (Timepoint: pre-vs. post-intervention fMRI) general linear model correcting for baseline was conducted with causal connectivity (standardized r score) between LDLPFC and each addiction network as the dependent variable.

To determine the intervention effects on relapse outcome, a Pearson Chi square test was conducted with relapse outcome (relapsed vs. abstained) as the dependent variable and intervention (active tDCS vs.

Table 3
Bilateral brain regions within each Addiction Domain.

	Regions in Each Addiction Domain (Koob & Volkow 2016; Kwako et al., 2018)			
	IS Consumption driven to experience reward	**NE** Consumption driven to avoid withdrawal and negative emotions	**EF/Go** Consumption driven by habit-induced craving	**EF/Stop** Consumption driven by poor inhibitory and affective control
Subcortical	Caudate Nucleus Accumbens Pallidum Putamen	Amygdala Caudate Diencephalon Nucleus Accumbens Pallidum Putamen	Caudate Nucleus Accumbens Pallidum Putamen	Amygdala
Cortical	Motor cortex[a]		Anterior Cingulate Cortex Inferior Frontal Cortex Insula[b] Medial Prefrontal Cortex	Anterior Cingulate Cortex Dorsolateral Prefrontal Cortex Inferior Frontal Cortex Medial Prefrontal Cortex Orbitopolar Frontal Cortex

IS, incentive salience; NE, negative emotionality; EF/Go, executive functioning go; EF/Stop, executive functioning stop.

[a] Including: Inferior and superior premotor, pre-motor, somatosensory, supplementary motor.

[b] Including: Anterior agranular insular complex, frontal opercular, insula granular, middle insula, posterior insula, posterior opercular.

sham) as the independent variable.

To determine whether the change in causal connectivity as a result of the intervention is associated with relapse outcome, a logistic regression was conducted with relapse outcome as the dependent variable, intervention type as the between-groups factor, and change in causal connectivity from LDLPFC to each addiction network as a covariate.

3. Results

Demographic, clinical and behavioral comparison between groups. There were no significant differences in age, education, number of women, age of AUD onset, AUD severity in the past six months, or length of abstinence before the baseline MRI session between intervention groups (Active tDCS vs. Sham) (Table 1). There were no significant group differences in psychiatric diagnoses (Table 4), changes in self-reported depression/anxiety (Supplementary Material G), medications (Supplementary Material H) or reversal learning performance changes (Table 5).

Relapse outcome. 17 participants relapsed (days to relapse since post-intervention MRI session: M = 15.36, SD = 10.49) and 43 participants remained abstinent by 1-month. By the 4-month follow-up timepoint 4 participants were not reachable anymore. 25 participants relapsed and 31 remained abstinent by the 4-month timepoint (days to relapse M = 44.2, SD = 42.42). Because Cox-proportional hazards regression revealed that women had higher likelihood of relapse than men (Supplementary Material F), analyses investigating intervention effects on relapse corrected for sex as a biological variable.

Intervention increased causal connectivity from LDLPFC to specific addiction networks. Analysis of variance (ANOVA) with change in average strength of connectivity as a dependent variable and Group as the independent variable correcting for baseline and sex revealed a significant Group (Active tDCS vs. Sham) x Time interaction in the average strength of connectivity from LDLPFC to the IS (LDLPFC-IS, Fig. 1a) and NE (LDLPFC-NE, Fig. 1b) networks. There was an increase in LDLPFC-IS (Fig. 2a) and LDLPFC-NE (Fig. 2b) causal connectivity in the active tDCS group and a decrease in the sham group. No significant intervention effect was found on LDLPFC-EF/Go or LDLPFC-EF/Stop causal connectivity. There were no significant causal connectivity group differences at baseline (Supplementary Material I).

Table 4
Counts of lifetime and current psychiatric diagnoses by intervention group.

Psychiatric Diagnoses[b]	Lifetime Diagnosis Count (%)			Current[a] Diagnoses Count (%)		
	Active tDCS (n = 31)	Sham (n = 29)	Chi[b] Sig.	Active tDCS (n = 31)	Sham (n = 29)	Chi[b] Sig.
MDD	13	14	p = 0.62	13	13	p = 0.81
GAD	14	9	p = 0.26	11	9	p = 0.72
PTSD	8	11	p = 0.31	9	10	p = 0.75
Social phobia	8	7	p = 0.89	7	7	p = 0.89
PD	6	7	p = 0.65	3	4	p = 0.62
Agoraphobia	3	3	p = 0.93	2	3	p = 0.59
ADHD	3	1	p = 0.33	3	1	p = 0.33

tDCS, transcranial direct current stimulation; Chi[b], Chi-Square; MDD, major depressive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; PD, panic disorder; ADHD, Attention deficit hyperactivity; p, significance (Sig.) probability value.

[a] Participants with current diagnoses were clinically stable.

[b] No lifetime or current diagnoses for the following disorders in the current sample: Dysthimia, Hypomania, Bipolar disorder (without psychosis episodes), Obsessive compulsive disorder, Antisocial personality disorder, Conduct disorder.

Table 5
Reversal Learning task performance change (post-intervention minus pre-intervention).

Performance change	All AUD (n = 60)	Active tDCS (n = 31)	Sham (n = 29)	Sig.
Mean reversal trial response time	−0.45	−0.48	−0.42	p = 0.79
Number of Reversals	3.38	2.19	4.45	p = 0.12

AUD, Alcohol Use Disorder; tDCS, transcranial direct current stimulation; p, significance (Sig.) probability value.

Causal connectivity change predicted 4-month *relapse status.* Logistic regression with binary relapse outcome as the dependent variable and change in LDLPFC-IS causal connectivity as the predictor, showed that LDLPFC-IS causal connectivity change was associated with a statistically significant increase in the odds of remaining abstinent during the 4-month follow-up period (Odds Ratio = 2.896; p = 0.035; after correcting for baseline and sex: Odds Ratio = 1.245; p = 0.060). A general linear model analysis correcting for sex and baseline showed a Group (Abstainers vs. Relapsers) x Time interaction effect on LDLPFC-IS (Fig. 3) causal connectivity strength. An ANOVA with Group (Abstainers vs. Relapsers at the 4-month follow-up period) as the independent variable and causal connectivity change as a dependent variable -correcting for sex and baseline-resulted in a significant group difference in the LDLPFC-IS (Fig. 4) networks. The effect was characterized by increased connectivity in the Abstainers' group and a decrease in the Relapsers' group. There were no significant findings in the NE, EF/Go or EF/Stop networks.

While change in causal connectivity predicted relapse status, baseline causal connectivity did not. Binary logistic regressions with relapse status both at 1- and 4-month follow-up as dependent variables and causal connectivity at baseline as predictors were not significant ($p > 0.05$). Linear regressions with time to relapse and length of abstinence as dependent variables and causal connectivity at baseline as predictors showed no significant results ($p > 0.05$). Baseline causal connectivity or causal connectivity change from pre-to post-intervention timepoints was not significantly associated with history of alcohol use variables (Table 1). There were no significant causal connectivity differences at baseline between abstainers and relapsers (Supplementary Material J).

Intervention effects on relapse outcomes. Pearson Chi square revealed that the probability of relapsing in the active tDCS group (19%; n = 31) was cut by half when compared to the sham group (38%; n = 29) (Fig. 5). Because relapse rates were different between men and women (Supplementary Material F), we conducted the same analyses splitting the sample by sex. There was a significant intervention effect on relapse rates in women (Fig. 6a), so that the probability of relapsing in women who received active tDCS (9.1%; n = 11) was cut by a factor of 5 when compared to women who received sham (50%; n = 10). Men (n = 39) did not show a significant effect (Fig. 6b).

tDCS Side Effects Questionnaire. Average ratings on the questionnaire were <1 (mild) for all symptoms at each timepoint. There were no significant changes from pre-to post-tDCS session, and there were no differences between active tDCS and sham groups for any symptom.

4. Discussion

The present study was designed to address the critical need for brain-based interventions that reduce relapse in alcohol use disorder (AUD). We investigated whether a non-invasive neuromodulation intervention combining transcranial direct current stimulation (tDCS) and cognitive training had an effect both on brain networks known to support abstinence and on subsequent relapse rates. While previous studies have reported tDCS effects on brain functional connectivity or clinical outcomes in AUD separately, the present study adds to the literature by

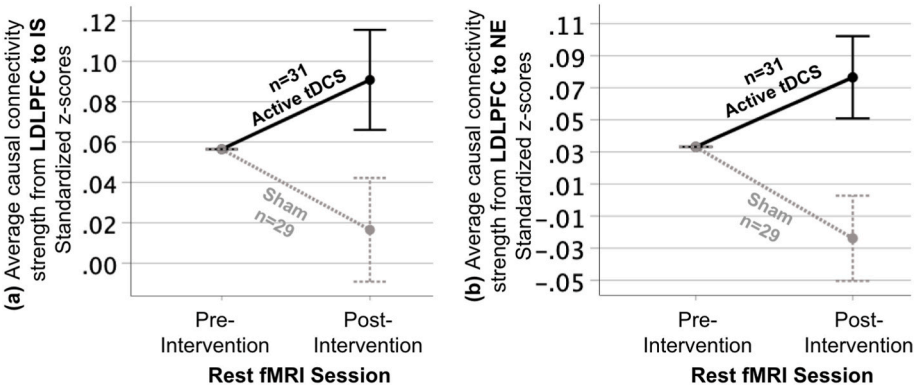

Fig. 1. Intervention effects on causal connectivity strength. Repeated measures general linear model analysis correcting for baseline showed a group (active tDCS vs. Sham) x time (pre-vs. post-intervention) interaction effect of average causal connectivity strength from LDLPFC (tDCS anode site) to the: **(a)** IS - incentive salience ($F(1,56) = 4.310$, $p = 0.042$) and **(b)** NE - negative emotionality ($F(1,56) = 7.378$, $p = 0.009$) addiction networks. No significant interaction was found in LDLPFC-EF/Go and LDLPFC-EF/Stop causal connectivity Error bars: ±1 standard error. tDCS, transcranial direct current stimulation; LDLPFC, left dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging.

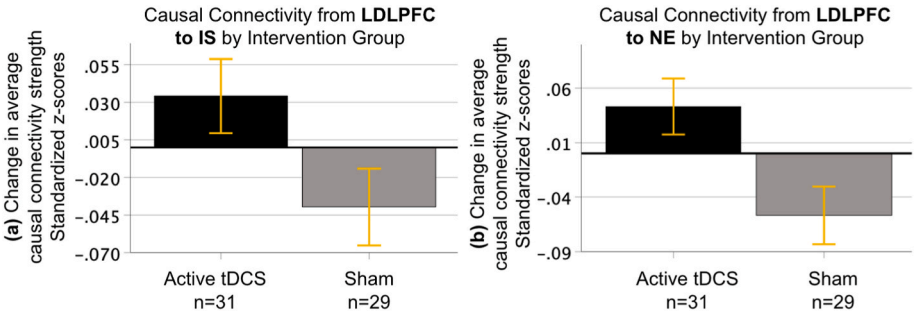

Fig. 2. Change in causal connectivity strength by intervention group. Significant effect of group (Active tDCS vs. Sham) in which those assigned to the active tDCS group showed an increase in causal connectivity strength from LDLPFC to **(a)** incentive salience ($F(1,59) = 4.331$, $p = 0.042$) and **(b)** negative emotionality ($F(1,57) = 7.320$, $p = 0.009$) addiction networks. Those randomly assigned to the sham group showed a decrease in causal connectivity. LDLPFC-EF/Go and LDLPFC-EF/Stop causal connectivity did not show a significant group effect. Error bars: ±1 standard error. tDCS, transcranial direct current stimulation; LDLPFC, left dorsolateral prefrontal cortex; IS, incentive salience; NE, negative emotionality.

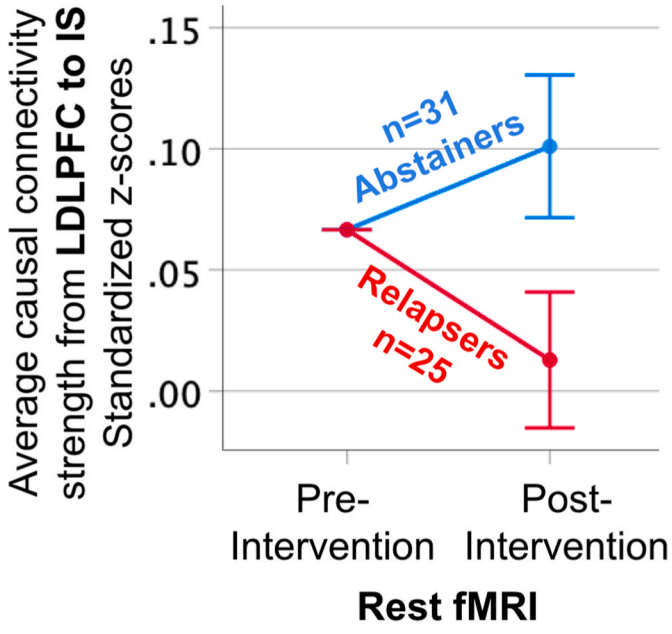

Fig. 3. Causal connectivity changes by subsequent relapse status at the 4-month follow-up timepoint. Repeated measures general linear model analysis correcting for baseline and sex showed a group (Abstainers in blue vs. Relapsers in red) x time (pre-vs. post-intervention) interaction effect of average strength of connections from LDLPFC to the incentive salience ($F(1,53) = 4.721$, $p = 0.034$). Causal connectivity from LDLPFC to the other addiction networks (NE, EF/Go and EF/Stop) showed a similar pattern, but not significant. Error bars: ±1 SE. tDCS, transcranial direct current stimulation; LDLPFC, left dorsolateral prefrontal cortex; IS, incentive salience; fMRI, functional magnetic resonance imaging. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

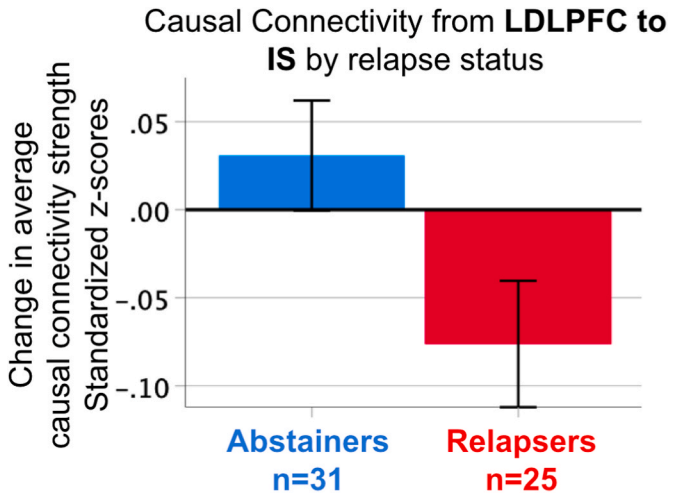

Fig. 4. Change in causal connectivity strength by subsequent relapse outcome. Significant effect of group (subsequent Abstainers in blue vs. Relapsers in red) in which those who maintained abstinence over the 4-month follow-up period (Abstainers - blue bar) showed an average increase in causal connectivity strength from LDLPFC to the incentive salience ($F(1,57) = 5.056$, $p = 0.029$)). Those randomly assigned to the sham group showed a decrease in LDLPFC-IS causal connectivity. Causal connectivity from LDLPFC to the other addiction networks (NE, EF/Go and EF/Stop) showed a similar pattern, but not significant. Error bars: ±1 standard error. LDLPFC, left dorsolateral prefrontal cortex; IS, incentive salience. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

providing important converging evidence under one clinical trial. Our results showed that the change in average strength of causal connectivity (specifically from LDLPFC to IS) as a result of active tDCS explains subsequent relapse outcome. The present study further adds to the

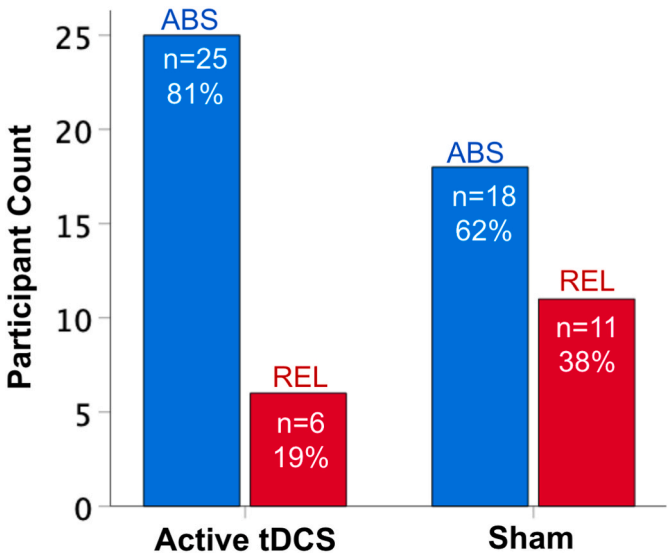

Fig. 5. Intervention effects on relapse rates. The probability of relapse in those randomly assigned to receive active tDCS (n = 31) was cut by half (19% probability) when compared to those randomly assigned to receive sham (n = 29; 38% probability) (Pearson Chi Square = 2.55; p = 0.11; Phi effect size = 0.21).

literature (i) by using recently developed analysis methodologies -causal connectivity analysis-to determine the directional influence of identified connections and (ii) by providing evidence of potential sex-dependent intervention effects on relapse rates.

4.1. tDCS induced causal connectivity changes

Current findings provide two important pieces of evidence regarding tDCS effects on brain connectivity changes. First, our results show that the tDCS intervention increased the strength of connections from the area below the tDCS anode (LDLPFC) to addiction networks that we previously found to support abstinence [9]. The biochemical mechanisms underlying DLPFC stimulation using tDCS have been previously demonstrated using positron emission tomography (PET) imaging, with important evidence that tDCS on DLPFC induces neurotransmitter release in subcortical areas, that is, increased extracellular dopamine of the striatum [38]. Neuroimaging data collected before and after the intervention allowed us to identify causal connections being modulated with tDCS. Present findings extend a previous report of tDCS's effects on global efficiency in AUD [2] by narrowing down the findings of specific tDCS modulation on the direct influence from LDLPFC to theoretically defined addiction networks known to support abstinence [9]. Our results showed that active tDCS specifically enhanced the average strength of connections from LDLPFC to the IS and NE addiction networks (Figs. 1 and 2). That is, the average strength of LDLPFC-IS and LDLPFC-NE causal connectivity increased from pre-to post-intervention only for those that received active tDCS, and decreased for those who received sham.

Causal connectivity reductions observed in the sham group (Figs. 1 and 2) are intriguing. First, these reductions could denote a normal declining progression of connectivity decay in those that do not undergo active tDCS, as found in another AUD tDCS study (Fig. 2 in Ref. [2]). Frontal-striatal connectivity reduction has been recently reported in individuals with AUD as a characteristic progression of the disorder [39]. Our current findings show this connectivity reduction is particularly evident in those that subsequently relapsed (Fig. 3), a finding that is in line with a previous longitudinal study in which we reported that connectivity reduction during early abstinence was a marker of subsequent relapse [7]. To further explore this premise, we conducted analyses to determine the association between causal connectivity changes and length of abstinence. We found that causal connectivity changes were significantly positively correlated with length of abstinence over the 4-month follow-up (LDLPFC to EF/Go: Spearman rho = 0.323, p = 0.015; LDLPFC to EF/Stop: Spearman rho = 0.335; p = 0.012). That is, LDLPFC-EF/Go and LDLPFC-EF/Stop causal connectivity decrease was associated with shorter time to relapse over the 4-month follow-up period. These findings, together with the literature reporting that reduced connectivity is a marker for relapse in addiction (e.g. Refs. [6,9,40–43]), suggest that the observed causal connectivity reduction (from LDLPFC to IS and NE) in the sham group may be characteristic of the addiction cycle, particularly for those that are more likely to relapse. Second, to further examine whether the observed causal connectivity reductions in the sham group is a generalized reduction in connectivity, we conducted the same CDA analysis (as described in Supplementary Material B), reversing the direction. That is, we examined causal connectivity (i) from IS to LDLPFC and (ii) from NE to LDLPFC. There was no group × time interaction in causal connectivity changes in the reverse direction (Fig. 7). The causal influence from addiction networks (both IS and NE) to LDLPFC increased for both active tDCS and sham groups. This time-dependent increase of bottom-up signaling (IS→LDLPFC and NE→LDLPFC) during abstinence could represent a concept known as "incubation" in preclinical and clinical addiction research [44–47]. During incubation, bottom-up signaling progressively increases during abstinence, driving increases in cue-induced craving, and increased risk of subsequent relapse [46,47]. On the other hand, we found that the causal influence *from* LDLPFC *to* addiction networks (IS and NE) does change differentially across intervention groups (Figs. 1 and 2). The specific increase in LDLPFC→IS causal connectivity for those

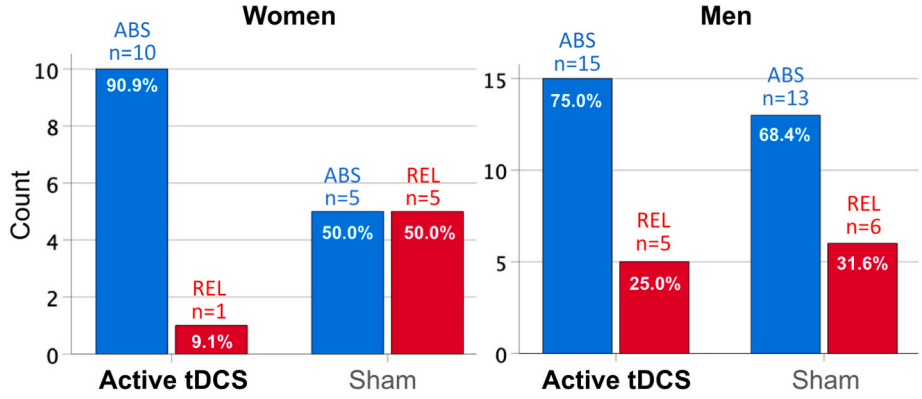

Fig. 6. Intervention Effects on Relapse Outcomes by Sex as a Biological Variable. Pearson Chi square analysis with the sample split by sex as a biological variable. **(a)** Women showed significant intervention effects on relapse rates (Pearson Chi Square = 4.30; p = 0.038; Phi effect size = 0.452), while **(b)** men did not (Pearson Chi Square = 0.21; p = 0.648; Phi effect size = 0.073).

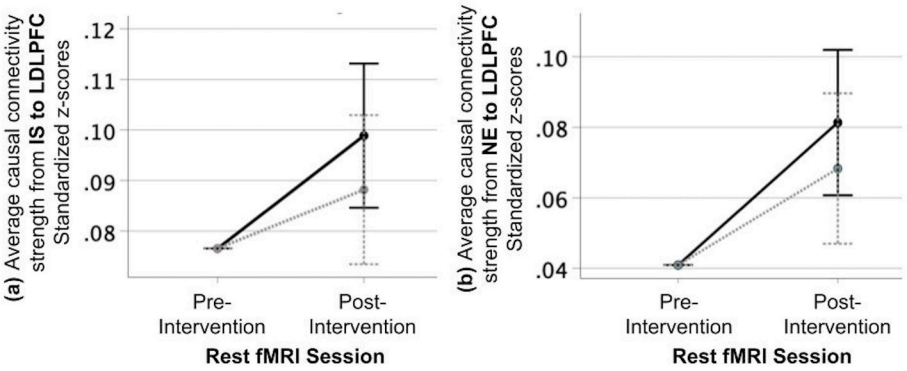

Fig. 7. Reversing causal connectivity analysis showed no intervention effects. Repeated measures general linear model analysis correcting for baseline showed no significant group (active tDCS vs. Sham) x time (pre-vs. post-intervention) interaction of average causal connectivity strength **(a)** from incentive salience network to the LDLPFC ($F(1,56) = 0.271$, $p = 0.605$) and **(b)** from the negative emotionality network ($F(1,56) = 0.192$, $p = 0.663$) to the LDLPFC. Error bars: ±1 standard error. tDCS, transcranial direct current stimulation; LDLPFC, left dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging.

assigned to receive tDCS on LDLPFC (Figs. 1 and 2), potentially facilitates LDLPFC influence (executive control) on bottom-up signaling and may underlie the ability to remain abstinent (Figs. 3 and 4). Conversely, since those assigned to receive sham did not undergo LDLPFC stimulation, DLPFC's causal influence on bottom-up signaling decreased over time, a pattern found in those that subsequently relapsed (Figs. 3 and 4). This interpretation is in line with the literature suggesting excessive bottom-up and reduced top-down signaling in substance use disorders (e.g. Refs. [48–50]). While these hypotheses are derived from our results and existing literature, they need to be further investigated.

The second key finding regarding tDCS effects is that the montage of F3 anode and F4 cathode specifically increased the causal connectivity strength from LDLPFC to the IS and NE addiction networks. Because we did not find significant intervention effects when exploring right DLPFC (Supplementary Material K) or primary visual cortex **(Supplementary Material L)** as sources in the causal connectivity analysis, our intervention seems to be specific to inducing changes on the causal connectivity from the location of the tDCS anode (LDLPFC) to these two specific addiction networks (IS and NE). These results are promising evidence of the modulatory effects of non-invasive neuromodulation, specifically from an executive control cortical region (LDLPFC) to theoretically defined addiction networks, which the literature has suggested to play a role in regulating reward processing and negative emotion [10,51–54].

4.2. tDCS effects on clinical measures in addiction

The present study extends our most recent cross-sectional neuroimaging findings [9] which reported that higher connectivity within these theoretically defined addiction networks measured during early abstinence was associated with reduced relapse rates and longer periods of abstinence. Our CDA analysis showed that the specific increase in LDLPFC-IS causal connectivity after 5 days of active tDCS was associated with increased odds of maintaining abstinence. The specificity of the causal connectivity from LDLPFC to the IS addiction network is consistent with our previous report [9] in which IS connectivity had the largest predictive power of subsequent relapse and time to relapse in AUD. In Koob and Volkow's formulation, brain regions listed as part of the incentive salience network play a role in the acquisition of conditioned cues acquired after chronic alcohol use [10,11,54]. Conditioned cues -associated with reward-become salient, and drive dopamine signaling [55,56] triggering strong motivation to seek a reward (e.g. alcohol) [10,54,57]. The premise that enhanced frontally mediated top-down control (LDLPFC) on incentive salience is crucial to support successful recovery [5,6,58] is supported by our recent [9] and current findings.

Our findings extend existing converging reports of promising effects of frontal stimulation in reducing relapse [1,3,12,14]. Previous studies have reported tDCS effects on relapse outcomes over various lengths of follow-up periods, such as over a 2-week [3] or 5-week follow-up period [14]. We are the first tDCS study that reported intervention effects over a 4-month follow-up period. New clinical trials designed to examine the durability of tDCS intervention in AUD need to be conducted with longer follow-up periods.

4.3. Considerations

Future trials designed to specifically address the following issues need to be conducted. First, while the statistical model comparing relapse rates between groups (active-tDCS vs. sham) showed a moderate effect in the whole sample (Fig. 5), this effect seemed to be driven by women (Fig. 6). Existing literature suggests that sex-dependent differences may be due to inherent anatomical differences mediating tDCS-induced neuroplasticity [59,60]. To determine if sex-dependent effects were due to potential sex differences in the magnitude of delivered electric field, we calculated the electric field delivered to LDLPFC, and found no differences between men and women (Supplementary Material M). Second, while this manuscript focused on causal connectivity from LDLPFC to addiction networks, our findings of no significant intervention effects on causal connectivity from other sources (right DLPFC Supplementary Material K or primary visual cortex Supplementary Material L) provide additional evidence of the intervention's specificity. Furthermore, we found that the effect is specific only to the causal connectivity direction from LDLPFC to IS and NE networks, because it was not found when examining the causal connectivity in the reverse direction (Fig. 7). Third, our results suggest that cognitive training alone (sham condition) was not sufficient to induce effects on causal connectivity change or treatment outcome. There is evidence that highest intervention effects on relapse rates are reached when combining a task requiring inhibitory control (i.e. Go/No-Go task) with active tDCS [3]. Growing evidence suggests that tDCS effects are maximized if delivered concurrently with (i) a variety of cognitive training tasks demanding engagement of different executive function domains (e.g. cognitive flexibility, inhibition, working memory, decision making) and (ii) tasks that continually challenge the participant's individual ability. Fourth, the current study was not conducted to empirically define the addiction networks. The criterion used here and previously [9] to define the putative addiction networks derived from the theoretical model of addiction [10,11,54] has not been empirically tested using rest fMRI in individuals with alcohol use disorder yet. This is an important topic for future large-scale studies. Finally, our strict criteria to define relapse (a single drink during follow-up period) was used to be consistent with our previous work (Camchong et al., 2013b, 2014, 2017, 2021) and to avoid heterogeneity across participant's relapse/abstinence cycles. While this criteria may be more stringent than what has been defined in other alcohol treatment outcome studies, we recorded a 72% and 55% rate of abstinence at the 1- and 4-month follow-up timepoints respectively.

5. Conclusion

Results from our longitudinal double-blind randomized clinical trial suggest that 5 days of LDLPFC stimulation delivered during early

abstinence (i) increased the causal connectivity from LDLPFC to addiction networks supporting abstinence -incentive salience and negative emotionality networks- and (ii) increased the odds of maintaining abstinence in individuals with AUD. More specifically, an increase in LDLPFC-IS connectivity after active stimulation was associated with increased odds of abstinence maintenance. The unexpected sex-dependent neuromodulation effects need to be further examined in larger clinical trials.

CRediT authorship contribution statement

Jazmin Camchong: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editingReviewing and Editing, Visualization, Project administration, Funding acquisition. **Donovan Roediger:** Methodology, Formal analysis, Data curation, Visualization. **Mark Fiecas:** Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Casey S. Gilmore:** Writing – original draft, Writing – review & editing. **Matt Kushner:** Writing – review & editing. **Erich Kummerfeld:** Methodology, Resources, Formal analysis, Writing – review & editing. **Bryon A. Mueller:** Data curation, Writing – review & editing. **Kelvin O. Lim:** Conceptualization, Software, Resources, Formal analysis, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.06.011.

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