Addiction history moderates the effect of prefrontal 10-Hz transcranial alternating current stimulation on habitual action selection

Theresa H. McKim,1 Samantha J. Dove,1 Donita L. Robinson,2,3,4 Flavio Fröhlich,2,4,5 and Charlotte A. Boettiger1,3,4,6

1Department of Psychology and Neuroscience, University of North Carolina, Chapel Hill, North Carolina; 2Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina; 3Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, North Carolina; 4Neuroscience Curriculum, University of North Carolina, Chapel Hill, North Carolina; 5Joint UNC-NCSU Department of Biomedical Engineering, Department of Cell Biology and Physiology, Neuroscience Center, and Department of Neurology, University of North Carolina, Chapel Hill, North Carolina; and 6Biomedical Research Imaging Center, University of North Carolina, Chapel Hill, North Carolina

Abstract

Individuals with substance use disorders (SUDs) transition more quickly from goal-directed to habitual action-selection, but the neural mechanisms underlying this phenomenon remain unclear. Data from animal models suggest that drugs of abuse can modify the neurocircuits that regulate action-selection, enhancing circuits that drive inflexible, habit-based stimulus-response (S-R) action-selection and weakening circuits that drive flexible, goal-directed actions. Here, we tested the effect of bilateral 10-Hz transcranial alternating current stimulation (10Hz-tACs) of the dorsolateral prefrontal cortex on action-selection in men and women with a SUD history and an age- and sex-matched control group. We tested the hypothesis that true 10Hz-tACS versus active sham stimulation would reduce perseverative errors after changed response contingencies for well-learned S-R associations, reflecting reduced habit-based action-selection, specifically in the SUD group. We found that 10Hz-tACS increased perseverative errors in the control group, but in the SUD group, 10Hz-tACS effects on perseverative errors depended on substance abuse duration: a longer addiction history was associated with a greater reduction of perseverative errors. These results suggest that 10Hz-tACs altered circuit level dynamics regulating behavioral flexibility, and provide a foundation for future studies to test stimulation site, frequency, and timing specificity. Moreover, these data suggest that chronic substance abuse is associated with altered circuit dynamics that are ameliorated by 10Hz-tACs. Determining the generalizability of these effects and their duration merits investigation as a direction for novel therapeutic interventions. These findings are timely based on growing interest in transcranial stimulation methods for treating SUDs.

NEW & NOTEWORTHY Treating the executive dysfunction associated with addiction is hampered by redundancies in pharmacological regulation of different behavioral control circuits. Thus, nonpharmacological interventions hold promise for addiction treatment. Here, we show that, among people with an addiction history, 10-Hz transcranial alternating current stimulation (10Hz-tACS) of the dorsolateral prefrontal cortex can reduce habitual actions. The fact that 10Hz-tACS can regulate behavioral flexibility suggests its possible utility in reducing harmful habitual actions.

addiction; alpha; goal directed; habitual; prefrontal

INTRODUCTION

Motivated action selection is governed by two distinct, competing systems: an outcome-insensitive, stimulus-driven habit system, and a goal-directed system (1). The motivated actions that define addiction include a repetitive drug use cycle, disregard for action consequences, and change-resistant seeking behaviors. These characteristics indicate shifts
away from goal-directed actions shaped by action-outcome contingencies (2) and toward habitual behavior, a learning outcome through which stimuli can come to drive heavily repeated, stereotyped actions (3). Although such shifts could reflect the fact that repeated exposure to drugs of abuse potentiates habitual-action circuits and alters associative learning behaviors (4–6), it could also reflect weak top-down control (7–10). Data suggest that weak top-down control can result from decreased prefrontal cortex (PFC) control over goal-directed behaviors, yielding habitual response strategies (11–13). In animals, drugs of abuse facilitate transition to habitual responding (6), and PFC inhibition leads to habitual cocaine seeking (14). Studies of addiction-related abnormalities in the neural circuitry of goal-directed and habitual control in humans are limited, with no brain stimulation studies including people with substance use disorders (SUDs).

Goal-directed and habit-based actions are distinguished in animal models by two behavioral tests typically employed in animal studies: outcome devaluation or contingency degradation (3, 15). Both procedures use operant training to associate an action with a reward. Such stimulus-response-outcome associations can be overtaken to promote habit-based responding. After establishing these associations, outcomes are devalued through either conditioned taste aversion or specific satiety of the reinforcer. Following outcome devaluation, action-selection is measured to determine whether behavior flexibly adapts to the changed outcome value (i.e., is goal directed) or is outcome insensitive (i.e., habitual). Contingency degradation is accomplished via an omission schedule of reinforcement (reward occurs when action is withheld) or by providing “free” rewards irrespective of actions; both methods diminish the association between the trained behavior and the outcome. Again, continued responding for the outcome during a test session indicates habitual behavior, whereas decreased responding indicates goal-directed action.

Initial investigations in humans to elucidate the neural mechanisms of goal-directed and habitual control of behavior were directly translated from paradigms used extensively in animal models and implicated the ventromedial PFC (vmPFC) in goal-directed action selection (16, 17), a relationship confirmed with the novel “fruit task” (11, 18). In parallel, studies of value-based decision-making have converged on the vmPFC as essential for representation of value in service of action selection and the dorsolateral PFC (DLPFC) as essential for goal representation, with increased goal-directedness associated with greater functional connectivity between the vmPFC and DLPFC (19).

Despite the initial utility of the paradigms described above, the construct of habit in humans has proved difficult to measure in laboratory settings (20, 21). Significant limitations include the length of training required to engender habitual responding, difficulty in equating experience with task stimuli and rewarding outcomes, and difficulty with equating reward with outcome value. For example, preexisting biases toward food stimuli and rewards mean that these are not readily amenable to successful value manipulation. Furthermore, both goal-directed and habitual responding can exist simultaneously as strategies to facilitate action selection. The coexistence of such behaviors illustrates the necessity of adjudication between actions to successfully navigate and adapt to the environment, a function commonly ascribed to the PFC (22).

Additional paradigms have been developed to test the relative contribution of goal-directed versus habitual-action selection in humans. A probabilistic multistep decision task is commonly used to determine whether action-selection strategy is model based, influenced by outcomes to update behavior to maximize reward, or model free, based on cached outcome value (23, 24). Model-based behavior is based on an internal model of the task environment and outcomes, akin to goal-directed actions, whereas model-free behavior has been proposed to reflect habit-based choice selection. Behavior in this task has been ascribed to frontostriatal circuits broadly, but specific activation loci can depend on task parameters (25–27). Furthermore, whereas habitual and goal-directed behaviors depend on separable neural circuitry, model-based and model-free strategies appear to recruit largely overlapping brain areas (28, 29). In contrast, our previous work used a deterministic stimulus-response (S-R) learning task, the Hidden Association Between Images Task (HABIT), to investigate the neural basis of S-R learning with fMRI (30) and to behaviorally distinguish individuals with a SUD history (31). The HABIT employs abstract visual stimulus sets with multiple manual responses and includes numerous task permutations, making it suitable for investigating effects of interventions on S-R learning and relearning. Participants are trained in an initial session and tested in a separate session that includes a response devaluation manipulation. The instructed response devaluation alerts participants that some S-R contingencies are changed and allows quantification of habitual responding after changed contingencies for both well-established S-R sets versus freshly learned S-R associations. Advantages of the HABIT include the ability to measure behavior as it unfolds over time, task-specific conditions in which general deficits in response inhibition can be controlled for post-devaluation, and the capability for assessment in multiple contexts, such as pharmacological or neurostimulation interventions.

Several behavioral studies of action-selection strategies in SUD populations have been published to date. For example, alcohol-dependent individuals show impaired model-based control without changes in model-free action selection (32). However, abstinent alcoholics have been shown to either show more model-free responding compared to controls (33, 34) or no change in model-based or model-free action selection (35, 36). In amphetamine addiction, model-free action selection predominates (37), and mixed SUD populations show elevated habit-based response selection (31, 38). Deficits in PFC activation during action selection are seen in alcohol-dependent participants, suggesting reduced goal-directed control over responding (33, 34). Moreover, reduced medial PFC activation during model-based decision making predicts relapse (35). Finally, accumulating clinical data suggest that cognitive capacity in the executive domain, which includes goal-directed action selection, predicts successful treatment adherence in substance use disorders (see Ref. 39 for recent review).

Despite extensive research and neural circuit manipulation in animal models investigating action selection pointing to the importance of the prelimbic cortex, the rodent homolog of the DLPFC (40), in goal-directed actions (41), few
comparable neural circuit manipulations have been carried out in humans, and none among people with SUDs. Findings from noninvasive brain stimulation studies in healthy controls are mixed. Transient inactivation of the right DLPFC with theta burst transcranial magnetic stimulation (TMS) during the two-step decision task shifts choice behavior toward a model-free strategy (42), whereas anodal transcranial direct stimulation (tDCs) of the right DLPFC showed no effect on model-based and model-free actions (43). Thus, further investigation of brain stimulation effects on goal-directed and habit-based actions are needed.

Transcranial alternating current stimulation (tACS) applies weak oscillating currents to a brain region of interest to modulate endogenous oscillations at the applied frequency (44, 45). tACS has been used to determine causal links between frontal function and human behaviors (46, 47), showing that frontal tACS can alter working memory (48, 49), creative and abstract thinking (50), cognitive control during decision-making under risk (51), reinforcement learning (52), and inhibitory control (53). Frontal regions exhibit a peak in alpha activity during wakefulness at ~10 Hz (54), and frontal alpha band (~7–13 Hz) activity is thought to be involved in top-down control (55, 56). Furthermore, studies measuring EEG and behavioral correlates of executive function demonstrate a relationship between frontal alpha and behavioral deficits in addiction (57–61). If alpha-tACS can promote goal-directed, top-down control over automatic learned responses, it would suggest therapeutic promise of tACS for SUDs.

Given evidence of altered alpha activity in addiction, and that alpha stimulation increases cognitive flexibility (50), we sought to test whether boosting DLPFC alpha power via tACS would facilitate goal-directed action selection and reduce habit-based actions. Specifically, we evaluated bilateral DLPFC 10-Hz tACS (10Hz-tACS) effect on action selection in our HABIT paradigm in adults with an SUD history and a group of age-, sex-, and IQ-matched controls by using a within-subject, double-blind, active sham-controlled study design.

MATERIALS AND METHODS

Participants

Healthy adults were recruited from the University of North Carolina (UNC) Chapel Hill campus and surrounding community via advertisements. Participants (n = 37) were aged 18–55 yr old with no known history of neurological disorders, no current psychiatric diagnoses or psychoactive drug or medication use (excluding nicotine, alcohol and caffeine), and an estimated IQ within the normal range (~80). Additional exclusion criteria included family history of epilepsy or seizures, current use of beta-blockers, brain implants/devices, colorblindness, history of brain surgery, or pregnancy. Participants were recruited into two groups based on whether they met Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria for past drug or alcohol dependence in a structured clinical interview (62); healthy controls with no history of substance or alcohol dependence (Control, n = 20) or a history of alcohol or substance dependence but current abstinence (SUD, n = 17). An additional four participants were recruited to the SUD group but were excluded from data analyses due to low IQ (n = 3) or technical failure during the behavioral task (n = 1). Participants in the SUD group were required to self-report ≥2 wk of drug/alcohol abstinence before the initial study session; mean duration of abstinence was 1.5 ± 2.5 yr. Participants were screened for psychoactive drug use (Biotechnostix, Inc., Markham, ON, Canada), including alcohol (FC-10; Liveloc Inc., Wheat Ridge, CO) at the start of each of the three study sessions. Each subject provided written informed consent as approved by the UNC Office of Human Research Ethics.

General Procedure

We used a randomized, double-blind, within-subjects design. Subjects participated in three sessions, with at least one night’s sleep between each session. Subjects were paid for their participation, including performance bonuses in the Test sessions. During Session 0, participants underwent a structured clinical interview, completed a battery of standard questionnaires (see Behavioral Inventories), followed by behavioral training on the computerized S-R learning task (see Behavioral Task); no stimulation took place during Session 0 (Fig. 1B, HABIT Training). Participants also completed the automated operation span (OSpan) working memory task (63). Learning and habitual responding was then tested during Sessions 1 and 2 (stimulation sessions). During the stimulation sessions, participants completed the initial task refresher and then HABIT Test session Part 1. Next, head measurement and electrode placement were performed, and participants completed Part 2 of the Test session while undergoing either 10Hz-tACs or active sham. During one of the two Test sessions, 10Hz-tACs was administered for 30 min; for the other session, 10Hz-tACs was administered for 5 min (active sham) at the beginning of the HABIT Test Part 2 (Fig. 1B). The active sham condition was chosen to improve blinding to the neurosensory effects of the stimulation parameters (64–66). Each participant received both active sham and true stimulation, with order counterbalanced, and randomized and balanced between study groups (Control and SUD).

The number of days that elapsed between the HABIT Training and first (Control: 3 ± 3 days; SUD: 5 ± 6 days; t(35) = −1.18, P = 0.25) and second (Control: 6 ± 3.5 days; SUD: 8 ± 6 days; t(35) = −1.45, P = 0.16) Test session did not differ between groups. The average time between stimulation sessions (Test sessions 1 and 2) was also not different between groups (Control: 2.5 ± 2 days; SUD: 3 ± 2.5 days; t(35) = −0.76, P = 0.45). At the end of the session, participants completed a questionnaire regarding sensations and experience of the stimulation session, and whether they believed they received stimulation (67).

Behavioral Inventories

We administered a number of standard questionnaires to quantify factors that could impact our results (see Table 1). We quantified alcohol use behavior with the Alcohol Use and Disorders Identification test (AUDIT) (68) and substance use behavior with the Drug Use Screening Inventory, Domain I (DUSI-I) (69) and the Drug Abuse Screening Test (DAST) (70). We calculated density of familial alcohol abuse using the Family Tree Questionnaire (FTQ) (71). Neuropsychological
questionnaires included the Barratt Impulsivity Scale (BIS-11) (72), the Beck Depression Inventory (BDI) (73), Rotter’s Locus of Control scale (LOC) (74), the State-Trait Anxiety Inventory (STAI) (75), the Thought Action Fusion scale (TAF) (76), the Antisocial Practices Scale (APS) of the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) (77), and the Perceived Stress Scale (PSS) (78). Education and occupation were quantified with the Barratt Simplified Measure of Social Status (BSMSS) (79). We estimated IQ with the Shipley Institute of Living Scale (SILS) (80).

**Behavioral Task**

The HABIT is a S-R learning and relearning task implemented in E-Prime 2.0 (PST Inc., Pittsburgh, PA) comprised of a HABIT Training session and a two-part HABIT Test session, which occurs on a subsequent day. Task details have been described previously (30, 31). In brief, abstract visual stimuli were presented on a color LCD screen, and subjects used a four-button keypad for manual response selection using the fingers of their dominant hand. As schematized in the lower part of Fig. 1A, stimuli were displayed briefly (750 ms) on the screen, and participants had 1 s from stimulus onset to make a response. After 1 s, feedback appeared on the screen (300 ms) indicating “correct,” “incorrect,” or “no response.” Participants learned through trial and error to associate stimuli with specific manual responses. During training, participants learned two sets of S-R rules to a criterion of ≥90% accuracy (FAM sets). The method of set construction is shown in the top of Fig. 1A. Briefly, a randomly generated $8 \times 8$ matrix was constructed for each set, and 10 individual stimuli were generated from this matrix using 10 different color maps of the same 10 isoluminant hues (Matlab 6.1; Mathworks, Natick, MA). Each member of the set shared no commonly colored squares but rather preserved the relationship between identically colored squares (30). Trials were structured into blocks, with each block containing 15 stimuli selected randomly from a pair of stimulus sets (set size: 10 each, for a total of 20 possible stimuli per block). Participants then returned to the laboratory after ≥1 night’s sleep to complete the Test session. In the Test session, participants demonstrated retention of previously learned (FAM) associations in a brief refresher run, and for the actual Test, blocks of the two FAM sets were interspersed with blocks composed of two newly introduced stimulus sets (Nov sets), to measure new S-R learning.

![Study Session HABIT Protocol](image)

**Figure 1.** Study protocol and example electrode montage and stimulation parameters for bilateral dorsolateral prefrontal cortex (DLPFC) 10-Hz transcranial alternating current stimulation (10Hz-tACs). A, top: graphical representation of stimulus set construction, showing 2 example sets. Random numbers are generated to create unique $8 \times 8$ matrices (left), and stimulus sets are created by filling each matrix according to 10 different color maps. The 10-color maps each use the same 10 colors, but in a different order (middle). Two example stimulus sets (set A and set B) constructed via this method are shown on the right. Each previously learned (FAM) and newly introduced stimulus (Nov) block consisted of a mixture of 2 such sets. Adapted from Boettiger and D’Esposito (30). Bottom: task schematic depicting 2 trials. Adapted from Ref. 31. B: participants are randomized to receive either true or active sham stimulation first during Hidden Association Between Images Task (HABIT) Test Part 2 in a within-subjects design. HABIT Test Part 2 task performance measures behavior after response devaluation, in which response contingencies change for both a highly practiced (FAM) and a newly learned (Nov) stimulus-response (S-R) set. For one session, 10Hz-tACs was administered for the duration of the HABIT Test Part 2 (30 min); for the other session, 10Hz-tACs was administered for 5 min (active sham) at the beginning of the HABIT Test Part 2. C: placement of electrode locations was based on the 10-20 system of head measurement. The sham stimulation condition used a 5-min, 2-mA peak-to-peak 10-Hz sine wave flanked by 10-s linear envelope ramps in and out for a total duration of 5 min and 20 s, following the methods in Ref. 50. True tACs stimulation used the same stimulation signal but lasted 30 min instead of 5 min.
Transcranial Alternating Current Stimulation

Alternating current stimulation was delivered by a NeuroConn DC Stimulator Plus (NeuroConn, Ilmenau, Germany) through three conductive rubber electrodes (CarboStim; Medstim Inc., Wabasha, MN). Participants underwent head measurement according to the international 10–20 system to place the three electrodes over the apex of the head (Cz) and the prefrontal cortex bilaterally (F3 and F4; Fig. 1C). Two electrodes (4.45 ± 4.45 cm) were placed at F3 and F4, while the third, reference electrode (4.45 ± 9.53 cm) was placed at Cz; all three were securely adhered to the scalp with conductive paste (Ten20; D.O. Weaver, Aurora, CO); impedance was kept below 5 kΩ. The sham stimulation condition used a 5-min, 2-mA peak-to-peak 10-Hz sine wave flank by 10 second linear envelope ramps in and out for a total duration of 5min and 20 s, following the methods of Ref. 50. True TACS stimulation used the same stimulation signal but lasted 30 min instead of 5 min. The participant was instructed that they would receive both real stimulation and sham stimulation, the order of which was randomized for the study sessions; the researcher and the participant were kept blinded to the stimulation condition by preprogramming of the device settings by the principal investigator.

Data Analysis

We used accuracy as the primary index of task performance in the HABIT Test sessions. The HABIT is composed of six runs before response contingency change (Part 1), and an additional six runs after the contingency change (Part 2). We calculated accuracy in three time bins in Part 1 and three time bins in Part 2 by combining two runs (early, mid, and late). Where sphericity assumptions were violated for repeated-measures analyses, we applied a Greenhouse–Geisser correction. In addition to considering accuracy, after the S-R contingency change we also differentiated error types (perseverative responses, other incorrect responses) to measure response-selection strategies utilized by participants. As previously reported, perseverative errors reflect outcome-independent and thus habitual actions. For regression-based analyses, we also used difference in perseverative errors between sham and true stimulation as our dependent variable. We also collected reaction time data in each trial. We tested for group differences in demographic and psychometric variables with unpaired two-tailed comparison between groups. $P$ value represents result of $\chi^2$ test. Boldface indicates significant difference between groups.

## RESULTS

### Demographic and Psychometric Data

Demographic questionnaire measures demonstrated that there were no significant differences between the SUD and Control groups in terms of age, education, socioeconomic status (SES), estimated IQ, sex, or ethnicity (Table 1). As expected, there were significant differences between groups in substance and alcohol use, with higher scores on all measures in the SUD group, including degree of consequences of substance abuse (DAST), severity of problems associated with drug and alcohol use.

### Table 1. Sample demographics and psychometric data demonstrate groups are matched

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>SUD Group</th>
<th>t(df)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>38 ± 8</td>
<td>39 ± 9</td>
<td>−0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>17 ± 2</td>
<td>15 ± 3</td>
<td>1.86</td>
<td>0.07</td>
</tr>
<tr>
<td>SES</td>
<td>52 ± 21</td>
<td>56 ± 16</td>
<td>−0.50</td>
<td>0.62</td>
</tr>
<tr>
<td>Sex (%female)</td>
<td>40</td>
<td>41</td>
<td>0.005</td>
<td>0.94</td>
</tr>
<tr>
<td>Ethnicity (%nonwhite)</td>
<td>40</td>
<td>24</td>
<td>1.14</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Substance Use related</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUDIT Total</td>
<td>2.5 ± 1.9</td>
<td>10.4 ± 10.6</td>
<td>−3.00</td>
<td>0.008</td>
</tr>
<tr>
<td>Consumption</td>
<td>2.3 ± 1.6</td>
<td>4.6 ± 4.0</td>
<td>−2.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Dependence</td>
<td>0</td>
<td>1.8 ± 3.6</td>
<td>−2.07</td>
<td>0.055</td>
</tr>
<tr>
<td>Harm</td>
<td>0.2 ± 0.4</td>
<td>3.9 ± 4.3</td>
<td>−3.54</td>
<td>0.003</td>
</tr>
<tr>
<td>DUSH-I (%)</td>
<td>0.5 ± 0.8</td>
<td>11.1 ± 3.3</td>
<td>−13.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAST</td>
<td>1.0 ± 0.7</td>
<td>17.8 ± 6.9</td>
<td>−10.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FTQ density (%)</td>
<td>0.11 ± 0.14</td>
<td>0.33 ± 2.1</td>
<td>−3.81</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS</td>
<td>9.8 ± 3.6</td>
<td>13.4 ± 7.2</td>
<td>−1.84</td>
<td>0.08</td>
</tr>
<tr>
<td>DSH total</td>
<td>47.8 ± 15.4</td>
<td>60.6 ± 13.3</td>
<td>−2.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Attention</td>
<td>12.0 ± 3.2</td>
<td>14.6 ± 4.3</td>
<td>−2.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor</td>
<td>17.9 ± 5.5</td>
<td>22.8 ± 5.5</td>
<td>−2.71</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonsignificant</td>
<td>17.9 ± 7.8</td>
<td>23.1 ± 5.1</td>
<td>−2.35</td>
<td>0.02</td>
</tr>
<tr>
<td>LOC</td>
<td>9.2 ± 3.3</td>
<td>9.6 ± 3.7</td>
<td>−0.38</td>
<td>0.70</td>
</tr>
<tr>
<td>STAI-trait anxiety</td>
<td>32.4 ± 5.1</td>
<td>37.0 ± 9.4</td>
<td>−1.92</td>
<td>0.06</td>
</tr>
<tr>
<td>STAI-state anxiety</td>
<td>28.8 ± 6.4</td>
<td>33.0 ± 9.0</td>
<td>−1.68</td>
<td>0.10</td>
</tr>
<tr>
<td>TAF total</td>
<td>19.9 ± 13.7</td>
<td>17.0 ± 12.5</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>Moral</td>
<td>17.6 ± 11.9</td>
<td>15.9 ± 12.2</td>
<td>0.42</td>
<td>0.68</td>
</tr>
<tr>
<td>Self</td>
<td>1.7 ± 2.7</td>
<td>0.8 ± 1.5</td>
<td>1.18</td>
<td>0.25</td>
</tr>
<tr>
<td>Others</td>
<td>0.6 ± 1.8</td>
<td>0.2 ± 0.8</td>
<td>0.79</td>
<td>0.43</td>
</tr>
<tr>
<td>MMPI-APS</td>
<td>6.1 ± 4.4</td>
<td>7.6 ± 3.2</td>
<td>−1.22</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSPAN score</td>
<td>38.1 ± 16.9</td>
<td>38.1 ± 16.8</td>
<td>0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>OSPAN total</td>
<td>56.1 ± 12.6</td>
<td>53.8 ± 14.3</td>
<td>0.50</td>
<td>0.62</td>
</tr>
<tr>
<td>Accuracy errors</td>
<td>7.2 ± 5.2</td>
<td>5.5 ± 3.5</td>
<td>1.16</td>
<td>0.25</td>
</tr>
<tr>
<td>Math errors</td>
<td>8.7 ± 7.3</td>
<td>7.1 ± 3.6</td>
<td>0.84</td>
<td>0.41</td>
</tr>
<tr>
<td>Speed errors</td>
<td>1.5 ± 2.5</td>
<td>1.5 ± 1.4</td>
<td>−0.04</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD. AUDIT, Alcohol Use Disorders Identification Test; BIS, Barratt Impulsivity Scale; DAST, Drug Abuse Screening Test; DUSI-I, Drug Use Screening Inventory, Domain 1; FTQ, Family Tree Questionnaire; IQ, intelligence quotient; LOC, locus of control; MMPI-ASP, Minnesota Multiphasic Personality Inventory-Antisocial Practices scale; OSPAN, operation span; PSS, perceived stress scale; SES, socioeconomic status; SILL, Shipley Institute of Living scale; SUD, substance use disorder; STAI, State-Trait Anxiety Inventory; TAF, Thought Action Fusion scale. Reported $P$ values reflect the results of unpaired two-tailed comparison between groups. Boldface indicates significant difference between groups.
or second (70% accuracy; blocks to criterion did not differ by group (FTQ density; Table 1). The SUD group reported higher levels of trait impulsiveness during the baseline Training session (Table 1), consistent with our previous study (31). Due to concerns that group differences in impulsivity could account for differences in performance, we tested for correlations between our main effect of interest (change in perseverative errors with true stimulation) and Barratt Impulsivity Scale (BIS) total or subscale scores. As no significant correlations were detected (min. $P > 0.58$, Spearman’s), BIS scores were not included as covariates in our reported analyses. We note that the SUD group tested here was somewhat older than the SUD group in our previous study. Groups were also matched in terms of working memory measured via the automated OSPAN (all $P > 0.25$; Table 1), ruling out generalized deficits in executive function that could impact task performance.

### Behavioral Performance during HABIT Training

During the HABIT Training session, participants were required to reach a performance criterion of 90% accuracy for each (FAM) set. Training to criterion took ~25 min, with no significant differences between groups in the average number of training blocks needed to learn the first ($t_{(35)} = -1.95, P = 0.07$) or second ($t_{(35)} = -0.76, P = 0.45$) FAM set. Participants next completed a third practice version of the task, which switched between blocks of FAM sets 1 and 2 and were required to reach 70% accuracy; blocks to criterion did not differ by group ($t_{(35)} = 0.53, P = 0.60$). Thus, training experience and performance between groups were equivalent before returning for the HABIT Test sessions. Participants demonstrated retention of previously learned FAM sets by again reaching the performance criterion of 70% at the start of each Test session by repeating the practice version that included blocks of both FAM sets. Groups did not differ in the number of trials to reach this criterion in either the first ($t_{(35)} = -0.17, P = 0.87$) or second Test session ($t_{(35)} = -1.00, P = 0.33$).

### Stimulation Blinding and Subjective Effects of Stimulation

Chi-square analysis confirmed that the randomization order of the stimulation conditions was counterbalanced across groups ($\chi^2_{(1)} = 0.70, P = 0.40$). Participants were successfully blinded to the stimulation conditions, and blinding success did not differ between groups for either true 10 Hz-tACS (Control group: 12/20 correct; SUD group: 10/17 correct: $t_{(35)} = 0.005, P = 0.94$) or sham stimulation (Control group: 12/20 correct; SUD group 5/17 correct: $\chi^2_{(1)} = 3.46, P = 0.063$). Subjective report of sensations (questionnaire based on (67)) for active versus sham stimulation also did not differ between groups (all $P > 0.13$; Fig. 2).

### Test Session Part 1: Learning New S-R Sets and Execution of Familiar S-R Sets

We first assessed S-R learning and execution in Part 1 of the HABIT Test sessions (Fig. 1B; see METHODS for task detail). To do so, we conducted a mixed-model repeated-measures ANOVA with set-type (FAM/NOV), time (early, mid, late), and stimulation condition (true, sham) as within-subject factors and stimulation order (sham first, true first) and group (Control, SUD) as between-subject factors. Although no stimulation occurred during Part 1 of the Test sessions, we included stimulation condition to verify that Part 1 performance was matched. We found expected main effects of set-type, with higher accuracy for FAM versus NOV sets ($F_{(1,35)} = 128.02, P < 0.001, \eta^2 = 0.37$; Fig. 3), and time, with accuracy improving from early (0.70 ± 0.02) to mid (0.77 ± 0.02) to late (0.80 ± 0.02) runs ($F_{(1,43,47.25)} = 108.30, P < 0.001, \eta^2 = 0.10$; Fig. 3). We also found a significant set-type $\times$ time interaction ($F_{(4,4.47,36)} = 63.87, P < 0.001, \eta^2 = 0.05$), reflecting a greater improvement of NOV set performance over time (Fig. 3). We found no significant main effects of group, stimulation condition, or stimulation order on accuracy before the contingency changes (min. $P > 0.33$), and no interaction between stimulation condition and group ($P > 0.49$). Stimulation condition did interact with stimulation order ($F_{(1,33)} = 23.76, P < 0.001, \eta^2 = 0.06$), reflecting a nuisance session effect of greater accuracy during Test session 2.

![Figure 2](image-url)

**Figure 2.** Percentage of participants reporting sensations during true stimulation and sham stimulation. $t$ tests demonstrated no significant differences between groups for true (A) versus sham (B) stimulation based on ratings of sensations, showing similar subjective experience of both conditions ($n = 37$). SUD, substance use disorder.
FAM set learning (min. P = 0.5). Performance increased over time for the FAM sets (F(1,59,52.60) = 11.15, P < 0.001, η² = 0.05) from early (0.82 ± 0.02) to mid (0.85 ± 0.02) to late (0.85 ± 0.02) runs. We did find a trend for a minor interaction between time and group (F(1,59,52.60) = 3.16, P = 0.061, η² = 0.01), reflecting a slightly earlier accuracy plateau in the Control relative to the SUD group (Fig. 3). We observed a stimulation condition by stimulation order interaction (F(1,33) = 35.56, P < 0.001, η² = 0.32), again reflecting a nuisance effect of session. Consistent with our previous studies (30, 31), accuracy increased significantly with time for the NOV sets (F(1,39,45.09) = 119.84, P < 0.001, η² = 0.33; Fig. 3). We detected no significant main effects of group, stimulation condition, or order on NOV set learning (min. P = 0.29) nor an interaction between time and group (F(1,39,45.09) = 2.04, P = 0.15). We again found a nuisance interaction between stimulation condition and stimulation order (F(1,33) = 5.78, P = 0.022, η² = 0.07). In summary, consistent with prior findings (31), our groups showed equivalent S-R learning and execution before stimulation.

### Test Session Part 2: Post-Devaluation Performance on Familiar and Novel S-R Sets

To evaluate task performance post-contingency change, we first conducted a mixed-model ANOVA with within-subject factors of stimulation type (true or sham), set-type (FAM or NOV set), contingency change (yes or no), and time (early, mid, late), with group and stimulation order as between-subject factors. We detected significant main effects of time (F(1,64,53.19) = 95.77, P < 0.001, η² = 0.07; Fig. 4), reflecting accuracy improvement over time after response devaluation. We also found a significant main effect of set-type (F(1,33) = 28.64, P < 0.001, η² = 0.16), and contingency change (F(1,33) = 12.50,

---

**Figure 3.** Mean accuracy for previously learned (FAM) and newly introduced (NOV) sets by group during Hidden Association Between Images Task (HABIT) Test Part 1 before stimulation for each stimulation condition. Plots reflect performance before stimulus-response (S-R) contingency changes and before stimulation commenced in sessions where participants received true 10-Hz transcranial alternating current stimulation (10Hz-tACS; A), or active sham stimulation (B). Solid lines represent the control group (Control, n = 20); dashed lines represent the substance use disorder (SUD, n = 17) history group. A mixed-model repeated-measures ANOVA indicated that Familiar set (FAM; teal) performance starts high and remains high preceding both stimulation types (A and B), while Novel set (NOV; gold) performance improves over time as S-R associations are learned, with no significant differences between session types (true, vs. sham; A and B). We detected no main effect of group (SUD vs. Control) or of session type (true vs. sham) on FAM set execution before stimulation. Data plots depict raw accuracy values adjusted for session order; error bars represent SE.

**Figure 4.** Performance for previously learned (FAM) and newly introduced (NOV) sets after response devaluation during Hidden Association Between Images Task (HABIT) Test Part 2. Left column images depict performance during true stimulation; right column depicts performance during active sham. Top (A) depicts FAM sets; bottom (B) depicts NOV sets. A mixed-model ANOVA found that, overall, accuracy improved over time after response devaluation (P < 0.001). A significant contingency change × time interaction (P < 0.001) showed larger changes in accuracy post-devaluation for sets with changed response contingencies (Deval) relative to those that did not change responses (NonDeval). A: performance improved over time for the FAM sets post-devaluation. B: performance increased over time for NOV sets after response devaluation. Contingency change also interacted with time (P < 0.001), demonstrating larger changes in accuracy over time for sets with changed response contingencies post-devaluation (Deval, light green (left) and light blue (right)) relative to unchanged contingency sets [NonDeval dark green (left) and dark blue (right)]. There were no significant effects of stimulation condition or group. Control: n = 20, SUD, n = 17; error bars reflect SE. SUD, substance use disorder.
P = 0.001, \eta^2 = 0.03), but not of stimulation type, stimulation order, or group (all P’s > 0.22). We found a set-type \times time interaction (F(2,66) = 4.03, P = 0.022, \eta^2 = 0.03), reflecting larger changes in accuracy for NOV sets relative to FAM sets after devaluation. There was also a significant contingency change \times time interaction (F(1.64,5.42) = 25.41, P < 0.001, \eta^2 = 0.02) reflecting larger changes in accuracy post-devaluation for sets with changed response contingencies relative to those that did not change responses. As noted above, we did not find a main effect of stimulation on performance, but stimulation type did interact with stimulation order (F(1,33) = 4.94, P = 0.033, \eta^2 = 0.01), suggesting that order effects may have obscured the full effects of stimulation type. We did not find any significant main effects or interactions with group (all F’s < 2.273, all P’s > 0.14).

### Quantifying Habitual Responding: Perseverative Errors Post-Contingency Change

Following Part 1, participants completed the HABIT Test Part 2, in which S-R contingencies changed for one NOV set of stimuli and one FAM set (Fig. 1B). During Part 2, participants received either true 10Hz-tACS, or active sham stimulation, using a within-subjects, double-blind, order-counterbalanced design. To quantify the degree to which responses were habitual, we calculated the percentage of perseverative errors within each group. The Control group committed significantly more perseverative errors in the sham stimulation condition (M = 0.36, SE = 0.02; F(1,18) = 5.90, P = 0.026, \eta^2 = 0.23; Fig. 5A). In contrast, in the SUD group the proportion of perseverative errors was slightly, but not significantly, reduced under true 10Hz-tACS (M = 0.36, SE = 0.02), versus sham stimulation (M = 0.37, SE = 0.03; F(1,15) = 0.28, P = 0.60; Fig. 5A). We also found a significant interaction between stimulation order and stimulation condition specific to the SUD group (F(1,15) = 8.06, P = 0.012, \eta^2 = 0.35), demonstrating a nuisance effect of session, such that perseverative errors decreased from session 1 to session 2 regardless of stimulation order in the SUD group. This nuisance effect may account for the lack of significant main effect of group of on FAM perseverative errors, in contrast to our previous single session study, although the Control group in this study was also older and reported more state anxiety, which could also contribute (31).

Individual differences in true versus sham stimulation on FAM perseverative responding are illustrated in Fig. 5, B and C.

Considering the wide range in duration of substance abuse in our SUD group (M = 12.9 yr, median = 15 yr, range: 2–28 yr), we tested whether the duration of substance abuse correlated with the effect of stimulation on perseverative errors. To rule out concerns that duration of abstinence could drive any such effects, we determined that years of substance abuse did not correlate with duration of abstinence (Spearman’s ρ = −0.009, P = 0.97). Moreover, on the basis of reports of increased perseverative responding in people with a history of cocaine but not opiate addiction (81), we also noted that the years of substance abuse of the two participants who did not report a history of alcohol and/or cocaine abuse did not fall at the extremes but rather in the middle (8–9 yr) of our participants’ reported range. A hierarchical regression analysis found that years of substance abuse significantly predicted the effect of 10Hz-tACS on perseverative errors, even after controlling for any effects of stimulation order, age, and the proportion of perseverative errors in the sham stimulation condition (β = −0.357, t(32) = −2.74, P = 0.010; see Table 2 for full regression model data). Although interesting, this finding could simply reflect a group difference in stimulation effects. Thus, we repeated the same hierarchical regression including only the SUD group. We found that years of substance abuse predicted the effect of 10Hz-tACS on perseverative errors even more strongly than when considering the full sample, again controlling for any effects of stimulation order, age, and the proportion of perseverative errors in the sham stimulation condition (β = −0.411, t(32) = −4.63, P = 0.001; Table 3). This yields a robust partial correlation of r = −0.801 between years of substance abuse and change in perseverative errors during 10Hz-tACS. Thus, although 10Hz-tACS increased perseverative errors in the Control group, the longer a participant’s duration of substance abuse, the more 10Hz-tACS decreased perseverative errors in the SUD group (Fig. 6).

### DISCUSSION

This noninvasive brain stimulation study examining effects of 10Hz-tACS of the DLPFC on goal-directed and habitual action-selection produced several notable and unexpected findings. First, we replicated our previous findings that individuals with an SUD history show a comparable ability to execute and to learn new S-R associations (HABIT Part 1) to controls with no substance abuse history (31). Further replicating our previous study, we found no group differences in global performance during S-R relearning (HABIT Part 2), when some of the S-R contingencies changed. Together, these results indicate no impairment in goal-directed action selection in the SUD group and support the interpretation that stimulation did not change goal-directed actions. A novel finding is that bilateral 10Hz-tACs stimulation of the DLPFC altered habitual action-selection after some of the S-R contingencies were changed. Critically,
this effect depended on substance abuse history, particularly the duration of substance abuse. Specifically, true 10Hz-tACS increasingly reduced habitual actions in the SUD group with greater duration of past substance abuse. These effects of stimulation were specific to highly practiced S-R associations and were not observed in performance of newly learned S-R associations. This finding points to the specificity of stimulation effects on habitual actions, as opposed to the inhibition and reversal of recently acquired, and still goal-directed, responses. In contrast, 10Hz-tACS increased perseverative errors relative to sham stimulation in the Control group. Thus, we partially confirmed our prediction that 10Hz-tACS

**Table 2. Summary of hierarchical regression analysis for variables predicting change in habitual responding during true 10Hz-tACS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
</tr>
<tr>
<td>Stimulus order</td>
<td>-0.160</td>
<td>0.056</td>
<td>-0.435**</td>
<td>-0.126</td>
<td>0.053</td>
<td>-0.342*</td>
<td>-0.103</td>
<td>0.049</td>
</tr>
<tr>
<td>Age</td>
<td>0.004</td>
<td>0.003</td>
<td>0.184</td>
<td>0</td>
<td>0.003</td>
<td>0.006</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Sham PE</td>
<td>-0.753</td>
<td>0.275</td>
<td>-0.429*</td>
<td>-0.738</td>
<td>0.251</td>
<td>-0.420**</td>
<td>-0.008</td>
<td>0.003</td>
</tr>
<tr>
<td>Years of abuse</td>
<td>0.221*</td>
<td></td>
<td></td>
<td>0.365**</td>
<td></td>
<td></td>
<td>0.485**</td>
<td></td>
</tr>
<tr>
<td>R²</td>
<td>4.810*</td>
<td></td>
<td></td>
<td>7.504*</td>
<td></td>
<td></td>
<td>7.495*</td>
<td></td>
</tr>
</tbody>
</table>

Note: Predictive variables are centered at their means; n = 37 subjects. 10Hz-tACS, 10-Hz transcranial alternating current stimulation; PE, perseverative errors. *P < 0.05, **P < 0.01, ***P < 0.001.
would reduce habit-based response selection in people with SUDs, but this benefit was specific to those with longer substance abuse histories. What might underlie this group difference in response? One possibility is that individual alpha frequency (IAF) differed systematically with duration of substance abuse. Individual peak alpha frequency is 10 Hz on average but in fact is widely variable across individuals (82, 83). IAF is considered a stable trait (84, 85) that is highly heritable (86), and which correlates with cognitive function (84). Moreover, stimulation shifted above or below IAF by as little as 2 Hz can have qualitatively different effects on behavior (87). Thus, we speculate that 10-Hz stimulation may have been systematically shifted away from IAF as a function of substance abuse history.

The present results suggest that DLPFC stimulation at 10 Hz disrupted the ability of Control subjects to perform goal-directed responses and/or overcome well-learned S-R associations. These findings are surprising, given our rationale for selecting stimulation parameters in the alpha frequency range. The DLPFC is essential in regulating and engaging goal-directed behaviors (11, 88) and as a source of frontal alpha band oscillations (56), which have been suggested to increase when attention and gating of irrelevant environmental stimuli are necessary (89). It has further been posited that alpha activity is necessary for top-down control, a function commonly ascribed to the DLPFC (22). As SUDs have been characterized with frontostriatal circuit dysfunction (90), targeting the DLPFC with 10-Hz stimulation may remediate deficits in overcoming habitual responding by normalizing frontostriatal circuit function. Moreover, if IAF is shifted lower in the SUD participants relative to Controls, the enhancing effects of 10Hz-tACS may reflect a boost not to alpha power but to beta power, specific to the SUD group. This interpretation is lent support by data demonstrating a role for beta oscillations in top-down control (91, 92).

Although experimental evidence demonstrates that tACS entrains neuronal oscillators (45, 93), the possibility remains that the behavioral effects of 10Hz-tACS in our study may result in part from off-target effects. For example, the 10Hz-tACS could activate either the trigeminal nerve, which energizes the scalp and dura, or the auricular branch of the vagus nerve, each of which stimulate the locus coeruleus (94). Stimulation of the locus coeruleus would yield widespread forebrain release of norepinephrine, which could either impair or improve executive function, depending on individual baseline catecholamine signaling (95, 96). This possibility predicts that acute stress would promote habit-based responding in the HABIT, which has also been demonstrated in other paradigms measuring goal-directed and habit-based action selection (97–99). Further support for this theory comes from a recent report showing that effects of transcranial direct current stimulation are mediated by greater occipital nerve activation of the locus coeruleus (100). Future work will investigate whether this mechanism contributes to 10Hz-tACS effects on habitual action selection.

In conclusion, our observations of individual variability in 10Hz-tACS effects on perseverative behavior that is largely explained by SUD history may reflect a number of different underlying mechanisms. Thus, the present findings lay a

---

### Table 3. Summary of hierarchical regression analysis for variables predicting change in habitual responding during true 10Hz-tACS in SUD group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
<td>β</td>
</tr>
<tr>
<td>Stimulus order</td>
<td>-0.184</td>
<td>0.066</td>
<td>-0.552*</td>
<td>-0.137</td>
<td>0.045</td>
<td>-0.409**</td>
</tr>
<tr>
<td>Age</td>
<td>0.007</td>
<td>0.004</td>
<td>0.346</td>
<td>0.001</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Sham PE</td>
<td>-0.685</td>
<td>0.241</td>
<td>-0.685**</td>
<td>-0.169</td>
<td>0.152</td>
<td>-0.756***</td>
</tr>
<tr>
<td>Years of abuse</td>
<td>0.467*</td>
<td>0.644*</td>
<td>0.786***</td>
<td>19.289**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R²</td>
<td>0.467*</td>
<td>6.144*</td>
<td>0.786***</td>
<td>19.289**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F for ΔR²</td>
<td>21.459</td>
<td></td>
<td></td>
<td>21.459**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Predictive variables are centered at their means; n = 17 subjects. 10Hz-tACS, 10-Hz transcranial alternating current stimulation; PE, perseverative errors; SUD, substance use disorder. *P < 0.05, **P < 0.01, ***P < 0.001.

---

**Figure 6.** Change in perseverative errors with 10-Hz transcranial alternating current stimulation (10Hz-tACS) as a function of years of substance abuse. Graph depicts the partial regression of perseverative error change with 10Hz-tACS on years of substance abuse for the substance use disorder (SUD) group only (n = 17). This quantifies the variance in perseverative error change predicted by years of substance abuse after controlling for any variance accounted for by stimulation order, age, and baseline (sham session) level of perseverative error. Dotted lines indicate 95% confidence interval for the regression line.
foundation for future studies to probe the underlying neural bases of the behavioral effects of 10Hz-tACS to bilateral DLPFC. A better understanding of these mechanisms will facilitate development of novel methods for the application of tACS, including real-time feedback methods, which will have wide therapeutic applications for disorders characterized by aberrant neural oscillation frequencies, including addiction (53, 101). Moreover, understanding how tACS may be more precisely employed not only to reduce but also to enhance habitual action selection may have therapeutic benefit more broadly, as healthy habits, by their automatic nature, can robustly aid behavioral change (102).

ACKNOWLEDGMENTS

We thank G. Guo, J. Gershgorn, and M. Moore for assistance with data collection, and K. Grewen, M. Sheridan, K. Reissner, and M. Robertson for valuable comments and discussion.

GRANTS

This work was funded by NIH Grants KL2 RR-025746 and UL1 TR-000083, and the Foundation for Alcohol Research/ABMRF (C.A.B.), P60 AA-011605 (C.A.B. and D.L.R.), and by T32 DA-000073, and the Foundation for Alcohol Research/ABMRF (C.A.B.), P60 AA-011605 (C.A.B. and D.L.R.), and by T32 DA-000073, and the Foundation for Alcohol Research/ABMRF (C.A.B.) and P60 AA-011605 (C.A.B. and D.L.R.).

We thank G. Guo, J. Gershgorn, and M. Moore for assistance with data collection, and K. Grewen, M. Sheridan, K. Reissner, and M. Robertson for valuable comments and discussion.

DISCLOSURES

F.F. is founder, shareholder, and chief scientific officer of Pulvinar Neuro, which did not play any role in the study reported here. F.F. revised manuscript; T.H.M., S.J.D., D.L.R., F.F., and C.A.B. approved final version of manuscript.

AUTHOR CONTRIBUTIONS


REFERENCES

10HZ-TACS of DLPFC alters habitual responding.


but not chronic amphetamine use is associated with perseverative
obsessive compulsive disorder. 


