Title: Identifying neural predictors of response to cortical or striatal deep brain stimulation in a rodent model of alcohol drinking: Towards developing individualized therapies for alcohol use disorders

Authors: Angela M. Henricks[1], Lucas L. Dwiel[2], Nicholas H. Deveau[3], Amanda A. Simon[3], Alan I. Green[1,2,4], Wilder T. Doucette[1,4]

[1]Department of Psychiatry, Geisel School of Medicine at Dartmouth
[2]Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth
[3]Dartmouth College
[4]The Dartmouth Clinical and Translational Science Institute, Dartmouth College

Corresponding author: Angela M. Henricks, Ph.D.
1 Medical Center Drive, Lebanon, NH 03756
Angela.m.henricks@dartmouth.edu
Tel: 603-650-9636

Abstract

Alcohol use disorders (AUDs) affect a large proportion of individuals in the United States. Unfortunately, the current therapies to treat AUDs are largely ineffective. Deep brain stimulation (DBS) has been proposed as a promising therapy for AUDs, but the high individual variability in treatment response limits broader implementation of this approach. The corticostriatal circuit is key in processing the rewarding properties of alcohol and we hypothesize that we can identify neural features within this circuit that will predict individual response to DBS in order to maximize treatment outcomes. In the current experiment, local field potentials (LFPs) were recorded from the nucleus accumbens shell (NAcSh) and medial prefrontal cortex (mPFC) of male Sprague-Dawley rats (n=13). The impact of NAcSh and mPFC DBS on levels of alcohol consumption was subsequently evaluated. On a population level, DBS in either region failed to significantly alter alcohol drinking behavior due to high individual variability in response. However, when individual features of corticostriatal LFPs were used as predictors of alcohol drinking outcomes (decreasers, increasers, or nonresponders to DBS) for each rat using a machine-learning approach (lasso), response to DBS could be predicted with greater accuracy than expected by chance. These data suggest that individual differences in corticostriatal circuit activity prior to stimulation likely contributes to the variable responses to DBS therapy. Ultimately, we hope to use knowledge gained from these data to tailor DBS therapies to individuals, further enhancing treatment efficacy.

Introduction

More than 15 million adults suffer from an alcohol use disorder (AUD) in the Unites State alone (1). Unfortunately, current pharmacotherapies for treating AUDs are not effective in all individuals, leading researchers to investigate alternative treatments for excessive alcohol consumption. Deep brain stimulation (DBS), which was originally used to treat movement disorders such as Parkinson's disease, has recently been suggested as a potential therapy for psychiatric and substance use disorders (2). DBS, however, is associated with particularly high individual variability in treatment response, and the current inability to predict which individuals will maximally respond to DBS treatment inhibits large-scale use of DBS therapy for AUDs.

Previous research suggests that a history of alcohol use is associated with dysregulation in the corticostriatal circuit (3,4), including the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC). The NAc integrates cortical inputs and indirectly sends feedback to the mPFC (5), and is particular important in the motivating and rewarding properties of abused drugs (6). The mPFC is activated in response to reward-related cues, and it has been suggested that deficits in the ability to inhibit responses to drugs arises from reduced top-down control of the mPFC to striatal regions (7). Therefore, both the NAc and mPFC are important targets for DBS therapy aimed at treating AUDs.

However, clinical and preclinical investigations evaluating NAc or mPFC DBS treatment for excessive alcohol consumption have shown mixed results. One clinical study showed that while NAc DBS reduced alcohol craving in all 5 AUD patients treated, only 2/5 patients maintained long-term abstinence following treatment initiation (8). In preclinical models, high frequency DBS to the NAc shell (NAcSh) reduced alcohol drinking in both alcohol-preferring and outbred rats (9,10), but the latter study also showed significant individual variability in the magnitude of response to DBS. Although the vast majority of clinical and preclinical studies have only evaluated NAc DBS for addictive behaviors, recent preclinical research has focused on cortical stimulation to reduce depression, with some success (11). Furthermore, clinical studies using transcranial magnetic stimulation (TMS) have demonstrated that stimulation of PFC regions can reduce depression in treatment-resistant patients (12,13), but the latter study showed that only about 50% of the patients responded clinically to TMS treatment.

Considering that cortical stimulation can be administered in a non-invasive manner via TMS in clinical settings, the impact of cortical DBS on alcohol drinking behavior warrants preclinical investigation. However, in order to enhance treatment efficacy, it is imperative to determine which individuals will maximally respond to NAc or mPFC DBS therapy.

Therefore, in the current study, we recorded local field potentials (LFPs) from the corticostriatal circuit and then treated rats with high frequency NAcSh or mPFC DBS during alcohol drinking sessions. We hypothesized that there would be high individual variability in: 1) baseline levels of alcohol consumption; and 2) the behavioral response to NAc and mPFC DBS (specifically that some animals would decrease alcohol consumption, while others would increase or show no change in drinking amounts during DBS). We aimed to capitalize on this variability in order to identify neural features (as measured by LFPs in the corticostriatal circuit) that might predict behavior. By approaching AUDs from the perspective that they arise from underlying circuit dysfunction, we aimed to determine which individual rats would maximally respond to DBS therapies targeted to various corticostriatal regions in order to begin to enhance treatment efficacy for AUDs.

Methods

Animals

Male Sprague-Dawley rats (n=13) were purchased from Harlan (South Easton, MA, USA) and arrived on postnatal day 60. All animals were housed individually on a reverse 12-hour light cycle with *ad libitum* access to food and water. All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) and were approved by the Institutional Animal Care and Use Committee of Dartmouth College.

Electrode implantation

Electrodes were designed and constructed in-house and were similar to those used in our previous publication (14). Following one week of habituation to the animal facility, rats were anesthetized with isoflurane gas (4% induction, 2% maintenance) and mounted in a stereotaxic frame. Custom electrodes were implanted bilaterally targeting NAcSh (from bregma: DV -8mm; AP +1.2mm; ML +/-1.0mm) and mPFC (from bregma:

DV -5mm; AP +3.7mm; ML +/-0.75mm). Four stainless steel skull screws were placed around the electrode site and dental cement (Dentsply, York, PA, USA) was applied to secure the electrodes in place. Rats were allowed to recover for at least one week prior to being tethered to the recording apparatus and trained to consume a 10% alcohol solution. At the end of the experiment, rats were euthanized using CO_2 gas and brains were snap frozen in 2-methylbutane on dry ice. Tissue was stored at -20°C prior to histological analysis.

Alcohol consumption training

Rats were trained to drink 10% alcohol in a limited access paradigm. Three days per week (M, W, F) animals were transferred from their home cage to custom stimulation chambers, tethered to stimulation cables, and given free access to 10% alcohol for 90 minutes. Animal weights and the volume of alcohol consumed was measured following each session in order to calculate g/kg of alcohol consumed. Rats were allowed to drink while plugged in to stimulation cables, without stimulation, until stable baseline alcohol consumption had been achieved (less than 40% deviation from the baseline average over 3 sessions).

Local field potential recordings

Prior to DBS (but after exposure to alcohol), rats were tethered in a neutral chamber through a commutator to a Plexon data acquisition system while time-synchronized video was recorded (Plexon, Plano, Tx) for offline analysis during 2, 30-minute sessions. Data from the entire 30-minute recording were analyzed using established frequency ranges from the rodent literature and standard LFP signal processing to characterize the power spectral densities (PSDs) within, and coherence between brain regions (bilateral NAcSh and mPFC) for each animal using custom code written for Matlab R2015b.

A fourth order Chebychev type I notch filter centered at 60 Hz was applied to all of the data to account for 60 Hz line noise. The data was then down-sampled by a factor of five from 2 kHz to 400 Hz. A threshold of ± 2 mV was used to identify noise artifacts and remove data using intervals 12.5 milliseconds before and 40 seconds after the artifacts. To capture the power and coherence dynamics of the signal, we used only behavioral

epochs that were at least 3 seconds long. For epochs that were longer than 3 seconds, we segmented them into 3-second sections removing the remainder to keep all of the data continuous over the same amount of time.

PSDs were computed using MATLAB's *pwelch* function using a 1.6 second Hamming window with 50% overlap. The PSDs for each 3-second segment were then averaged together to get a single representative PSD for the 30 minute recording session. Total power (dB) per frequency range was calculated using the following ranges: delta (Δ) = 1-4 Hz, theta (θ) = 5-10 Hz, alpha (α) = 11-14 Hz, beta (β) = 15-30 Hz, low gamma (lγ) = 45-65 Hz, and high gamma (hγ) 70-90 Hz (15,16). To account for the 60 Hz notch filter, power values of frequencies from 59 to 61 Hz were not included in the sum. The power per frequency band was then normalized as a percent of the average total power of the signal from 1 to 90 Hz (beginning of Δ to end of hγ).

Coherence was computed using the function *mscohere* with a 1.3 second sliding Hamming window with 50% overlap. The average coherence between each pair of frequency bands from 1 to 90 Hz (excluding values corresponding to the notch filter) were used to normalize the average coherence of each frequency band within that channel pair.

Deep brain stimulation

To deliver stimulation, a current-controlled stimulator (*PlexStim, Plexon, Plano, TX*) was used to generate a continuous train of biphasic pulses (biphasic, 90 μsec pulse width, 130 Hz, 200 μA). We chose 130Hz stimulation because this frequency matches what was used in a clinical study of DBS for AUDs (8). The output of the stimulator (current and voltage) was verified visually for each rat before and after each stimulation session using a factory-calibrated oscilloscope (TPS2002C, Tektronix, Beaverton, OR). Stimulation was initiated immediately before rats had access to alcohol and turned off at the completion of the 90-minute stimulation session. Rats were exposed to NAcSh or mPFC DBS for 3 sessions in a counterbalanced fashion, followed by a washout period, such that all animals were exposed to both NAcSh and mPFC stimulation. During the washout periods, animals were again allowed to drink alcohol while plugged in to the stimulation cables but without stimulation turned on. It is important to note that a subset

of animals (n=7) also received stimulation to the NAcSh and mPFC at 20Hz with washout periods between the two different DBS parameters (data not shown). Figure 1 outlines the experimental timeline.

Statistical Analysis

Calculating the population-based response to DBS

The overall effect of DBS in the NAcSh or mPFC on amount of alcohol consumed was analyzed using a repeated measures analysis of variance (RMANOVA), with alcohol consumption during baseline or washout (defined as the average of the last 3 sessions prior to DBS) and the three DBS sessions as within-subjects factors. Individual response to DBS in the NAcSh or mPFC was calculated as percent change from baseline or washout and compared to the animal's individual variance. For each animal, individual variance in alcohol consumed was calculated for the last three sessions of baseline consumption and the last three sessions of the washout period. Rats were classified as responders to stimulation if the percent change from baseline in at least one stimulation session deviated at least one standard deviation from their individual variability, which allowed us to classified individual differences in responses to DBS. Rats were thus characterized as decreasers, increasers, or non-responders to DBS, which served as the outcomes for building prediction models using the LFP features.

Linking individual corticostriatal activity to DBS outcomes and baseline alcohol consumption

Each recording session produced 60 LFP features: 24 measures of power (6 frequency bands X 4 channels) and 36 measures of coherence (6 frequency bands X 6 channel combinations). We used a penalized regression method (lasso) in order to capture potential combinations of LFP features that correlated with stimulation outcomes. The Matlab package *Glmnet* was used to implement the lasso using a cross-validation scheme with 100 repetitions for each target-outcome pair. The accuracy of the models is reported as the average cross-validated accuracy. We repeated the entire above process on ten random permutations of the data for each response group. The distributions of accuracies from the observed data were then compared to those from the permuted data using a Mann-Whitney *U* test and then converting the *U* test statistic into a Cohen's d

effect size. To predict baseline alcohol consumption the same process was used except the outcome was a continuous variable (g/kg of alcohol consumed) rather than binomial (responder or nonresponder).

Verification of Electrode Placement

All rats were euthanized at the conclusion of the experiment and the brains were removed, prepared for cryostat sectioning, mounted, sectioned, and stained (thionine) for histological analysis.

Results

Categorization of rats as decreasers, increasers, or non-responders

As hypothesized, we observed significant heterogeneity in response to DBS treatment [similar to what others have shown (9)], allowing us to characterize rats as decreasers or increasers (collectively called "responders"), or non-responders to treatment. Responders to DBS were defined as those rats showing a significant change in alcohol consumption (defined as a percent change from baseline of at least one standard deviation outside of their individual variance) during at least one DBS session. Rats that showed both a significant increase and decrease to stimulation were placed in the category corresponding to their strongest response. For the NAcSh, 7/13 rats were categorized as decreasers, 4/13 rats were categorized as increasers, and the remaining rats (2/13) were categorized as non-responders (Fig. 2A). For the mPFC, 5/12 rats were categorized as decreasers, 6/12 rats were categorized as increasers, and the remaining rat was categorized as a non-responder (Fig. 2C). All animals included in the results had electrodes located within the target structures, and we observed no correlation between electrode coordinates and behavioral outcomes (Fig. 2B and 2D).

NAcSh or mPFC DBS does not significantly alter alcohol drinking on a population level

Due to electrode headcap failure, one rat did not receive mPFC DBS. Overall, a RMANOVA showed no effect of NAcSh [$F(3,36)=1.14$, $p=0.35$] or mPFC [$F(3,30)=1.79$, $p=0.17$] DBS on g/kg of alcohol consumed indicating that DBS in either region did not have an overall effect on alcohol consumption in this study (Fig. 3A and 3B).

Using an independent samples t-test, a subgroup analysis of baseline alcohol consumption in NAcSh decreasers indicated that rats that showed a reduction in alcohol consumption after NAcSh DBS were drinking significantly more alcohol at baseline (prior to DBS) compared to all other rats ($p<0.05$; Fig. 3C). A subgroup analysis of baseline alcohol consumption in mPFC decreasers compared to all other rats (using an independent samples t-test) did not show a significant difference in baseline alcohol consumption between the two groups ($p>0.05$; Fig. 3D).

LFPs from the corticostriatal circuit predicts response to NAcSh or mPFC DBS

Models built from corticostriatal circuit activity were able to outperform permuted data in predicting both increasers ($d = 1.14$; Fig. 4A) and decreasers ($d = 1.10$; Fig. 4B) to NAcSh DBS. Similarly, corticostriatal activity outperformed permuted data in predicting both increasers ($d = 1.15$; Fig. 4C) and decreasers ($d = 1.15$; Fig. 4D) to mPFC DBS. The baseline alcohol consumption level had a trend-level correlation with response to NAcSh DBS ($p = 0.09$), but had no relationship with response to mPFC DBS ($p = 0.14$).

LFPs from the corticostriatal circuit do not meaningfully predict baseline alcohol consumption levels

Models built from corticostriatal activity were able to outperform permuted data in predicting baseline alcohol consumption in all rats ($d = 0.69$; Fig. 4E), but it is important to note that the absolute error (0.4 g/kg) of the prediction model was greater than the baseline alcohol consumption of the majority of the rats. In other words, the majority of rats were consuming alcohol at levels lower than 4 mg/kg/session, indicating that our ability to predict baseline consumption levels may not be meaningfully applicable to future studies aimed at identifying which rats would be “high,” “moderate,” or “low” drinkers.

Discussion

Recent clinical and preclinical research has begun to assess the efficacy of DBS for reducing substance use, but high individual variability in responses to DBS requires that current research identifies those individual rats most likely to respond to treatment. Similar to findings from clinical experiments in alcoholic individuals (8), our preclinical study demonstrated significant variance in individual DBS response; approximately 50%

of animals showed a reduction in alcohol drinking following NAcSh or mPFC DBS. Importantly, measures of corticostriatal circuit activity also correlated with DBS outcomes, indicating that measuring corticostriatal activity prior to DBS can help identify: 1) which animals would respond to NAcSh or mPFC stimulation; and 2) the direction of the change in alcohol consumption (decrease or increase) DBS would induce. This study therefore provides important preliminary evidence supporting the use of corticostriatal circuit activity to predict responses to DBS, and this approach could be used to attempt to predict responses to DBS prior to subsequent alcohol exposure.

In the present study, responses to NAcSh and mPFC DBS could be predicted by baseline corticostriatal circuit activity, and decreasers to NAcSh DBS showed higher levels of alcohol consumption at baseline. However, while there was a trend for baseline alcohol consumption to predict DBS response (in the NAcSh), corticostriatal activity did not meaningfully predict baseline alcohol consumption (see Fig. 4F for summary of predictive findings). These data suggest that while the corticostriatal circuit contains relevant information for predicting DBS response, it does not contain enough information to predict baseline levels of alcohol drinking in our study. Information from other brain regions involved in addiction-related behaviors, such as the amygdala or orbital-frontal cortex (6), may contain additional neural information relevant to predicting baseline alcohol consumption levels. While we were unable to identify the sources of variation in baseline alcohol consumption, this study was not explicitly designed to identify and test all the sources of variantion that could impact alcohol drinking behavior in rats, and future studies will be needed to identify predictors of the observed variability in baseline drinking.

Overall, NAcSh DBS did not reduce alcohol consumption in our studies due to high variability in drinking behavior and response to DBS, but others have demonstrated that NAc DBS significantly reduces alcohol consumption in rats (9,10). These data, in conjunction with the present experiment, suggest that NAc DBS may be an effective treatment for alcoholism in a subset of individuals. The NAc is an important component of the limbic system, with reciprocal projections to other brain structures integral in reward-related behavior, including the mPFC (5). It is thus unsurprising that the NAc is a commonly proposed target for treating addiction-related behaviors using circuit based

interventions, and future studies should further pursue strategies to maximize treatment efficacy for NAc DBS.

To our knowledge, the present experiment is the first to assess the efficacy of mPFC DBS to modulate alcohol consumption in rats, though it has been investigated to alleviate treatment-resistant depression. AUDs and depression are highly co-morbid (17) and the neural circuits underlying both addiction and depression significantly overlap (18). Thus, the mechanisms underlying the efficacy of cortical stimulation to treat depression may also drive reductions in alcohol drinking behavior observed in a subset of rats (5/12) in this study. Importantly, a recent pilot study showed that TMS of the mPFC reduced craving and self-reported alcohol consumption in a group of alcoholic individuals (19). Since our work supports the therapeutic potential of mPFC DBS in a subset of individuals, and cortical stimulation can be achieved using non-invasive approaches (such as TMS), future clinical and preclinical research should further evaluate the efficacy of cortical stimulation for treating AUDs.

There are several limitations to consider in the present study that warrant future investigation. First, even animals classified as decreasers to DBS did not necessarily show reductions in alcohol consumption during every DBS session. Our classification of animals as decreasers, increasers, or nonresponders was based on whether the rat had at least one DBS session one standard deviation from their individual variance. Though our LFP data was able to predict individual response based on our categorization system, we acknowledge that rats could have been categorized in a variety of ways. Second, we aimed our mPFC electrodes to the infralimbic/prelimbic junction as we did not have an *a priori* hypothesis that one site would be more effective in reducing alcohol drinking over the other. Additionally, we did not observe any significant correlation between infralimbic/prelimbic placement of the electrodes and response to DBS, but future research should investigate whether these regions lead to distinct changes in alcohol drinking behavior. Lastly, though others have demonstrated that NAc or mPFC stimulation does not alter locomotor activity in rodents (20,21), we did not directly measure locomotor behavior, and it may be possible that DBS simply reduced locomotor activity in decreasers (or vice-versa in increasers). We also did not measure water intake during DBS, but others have demonstrated that NAc DBS does not affect this measure (22),

suggesting that any reductions in alcohol drinking behavior we observed (at least for NAcSh DBS) were not simply related to reductions in consummatory behavior in general.

Despite these limitations, data from this study highlight an important caveat impeding more widespread use of circuit-based therapies: highly variable treatment outcomes across individuals. The fact that approximately 50% of our rats did not show decreases in alcohol consumption during DBS treatment suggests that perhaps not all individuals respond to the same stimulation parameters. Indeed, other studies have compared the reward value of different stimulation parameters in rodents and suggested that different animals favor different simulation parameters (23). Thus, further advancement of DBS therapies requires that stimulation parameters (including electrode placement and frequency) be personalized based on an individual's unique brain structure and function. Our future work will attempt to predict which animals will be responders to NAcSh or mPFC DBS prior to alcohol exposure, and then test rats' behavioral response to DBS based on the previously determined categorization. Research in our laboratory currently aims to use preclinical models to demonstrate the value of personalizing DBS treatments through the use of relevant underlying neural circuit activity. We specifically aim to identify corticostriatal circuit activity correlated to underlying behavioral variation during behaviors of interest (like alcohol drinking) and then use identified circuit-based markers as a readout to assess the effect of different stimulation parameters. Ultimately, we hope to develop a method of adaptive DBS that will concurrently modulate stimulation parameters in response to changes in each individuals' neural circuit activity, allowing for more nuanced and individually tuned circuit based interventions for AUDs.

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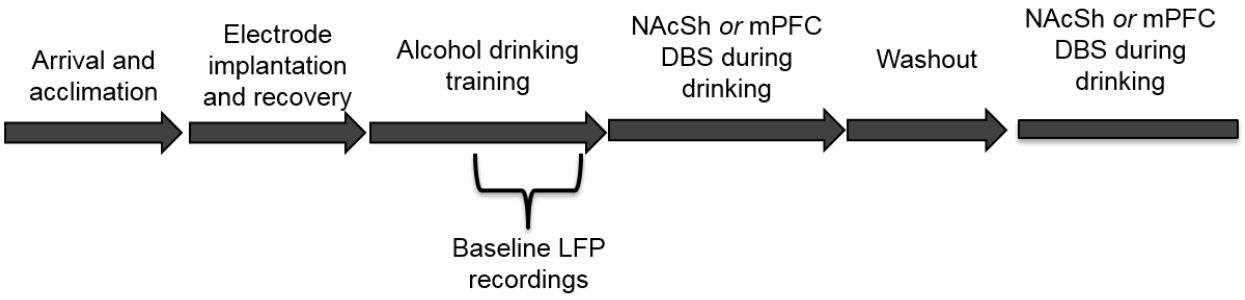
Figure captions

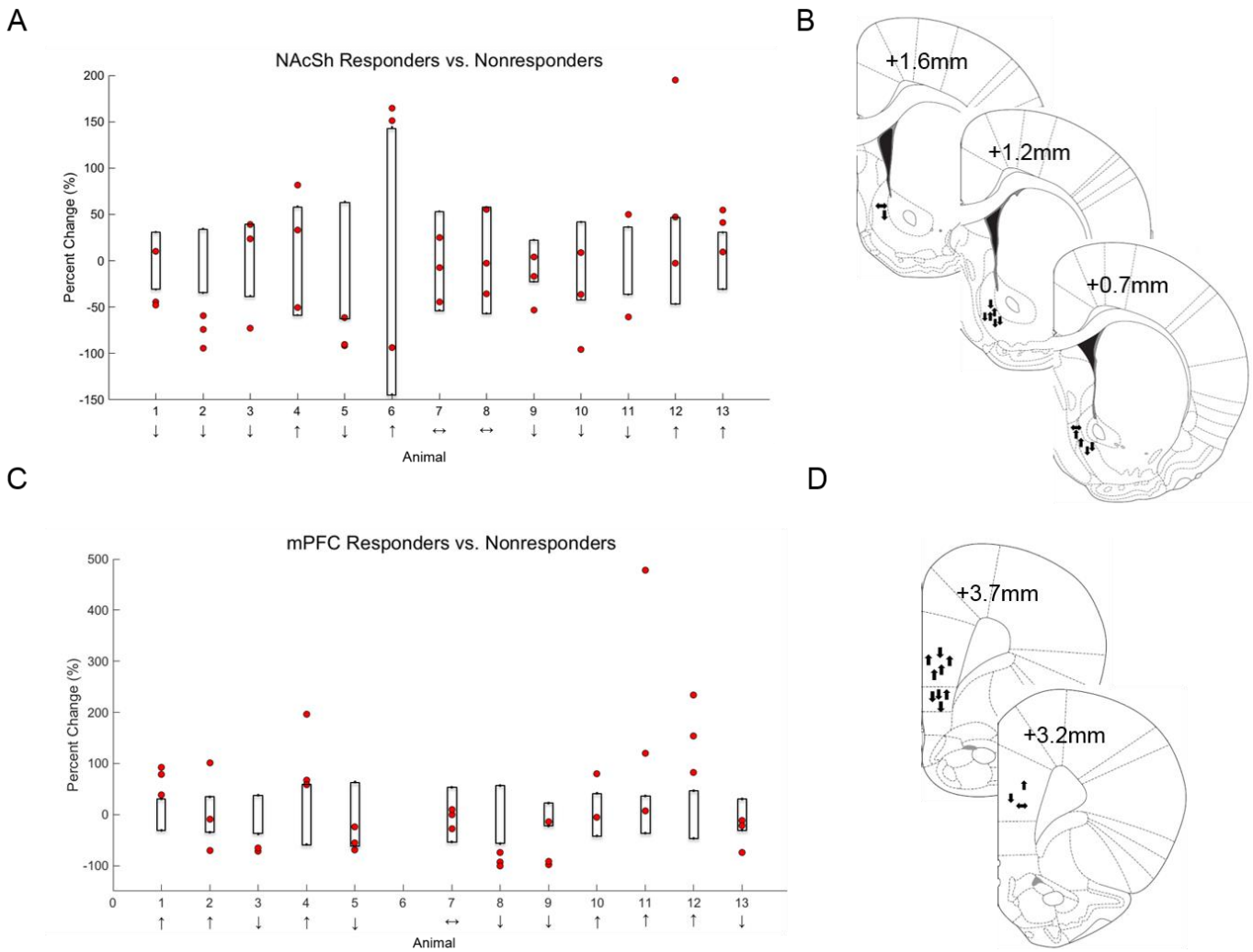
Figure 1. Experimental timeline.

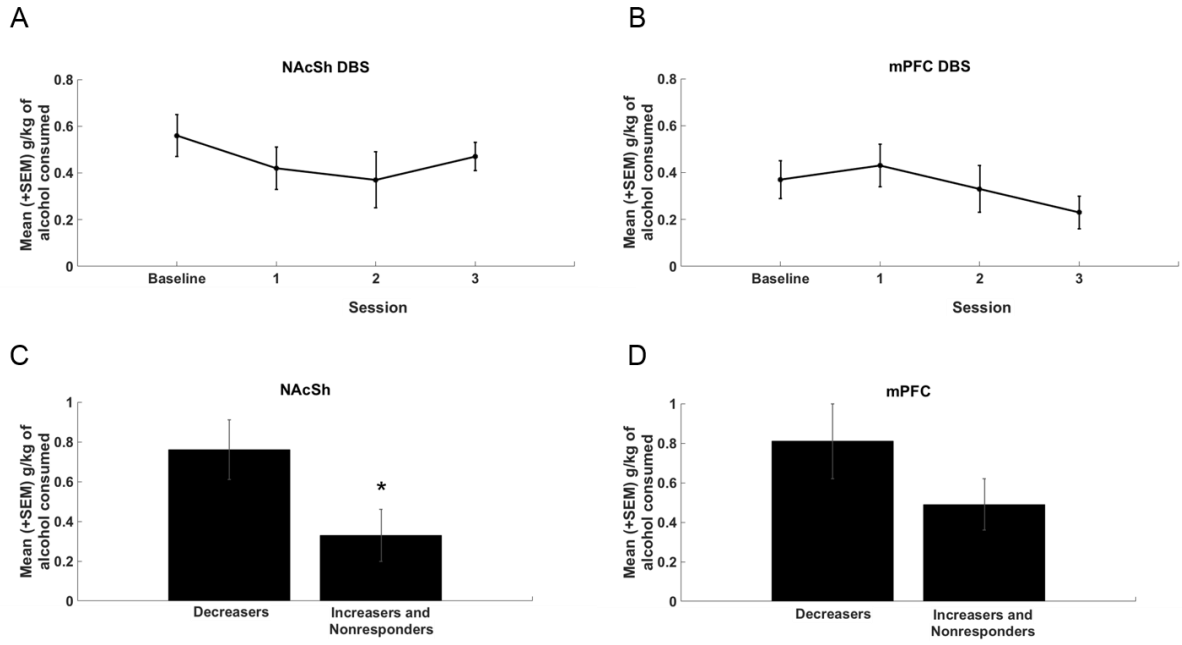
Figure 2. Categorization of animals as decreasers, increasers, or non-responders to DBS in the NAcSh (**A**) and mPFC (**C**). Boxes represent each rats' individual variance during non-DBS sessions. Red dots represent the percent change in alcohol drinking from baseline in response to DBS. Rats that showed a change (calculated as percent change) of at least one standard deviation outside of their individual variance in at least one DBS session were categorized as increasers (↑) or decreasers (↓). All other rats were categorized as non-responders (↔). Rats that showed both a significant increase and decrease to stimulation were placed in the category corresponding to their strongest response. All rats included in the statistical analysis had electrode locations within the bilateral NAcSh (**B**) and mPFC (**D**). Each rat is represented with an arrow indicating electrode placement and direction of response to DBS.

Figure 3. Population-based analysis of alcohol drinking behavior. NAcSh DBS did not significantly alter g/kg of alcohol consumed compared to baseline alcohol consumption (**A**). mPFC DBS did not significantly alter g/kg of alcohol consumed compared to baseline alcohol consumption (**B**). Rats showing a significant decrease in alcohol consumption to NAcSh DBS drank significantly more alcohol at baseline than all other animals (**C**). There were no significant differences in baseline alcohol consumption between decreasers to mPFC DBS and all other animals (**D**).

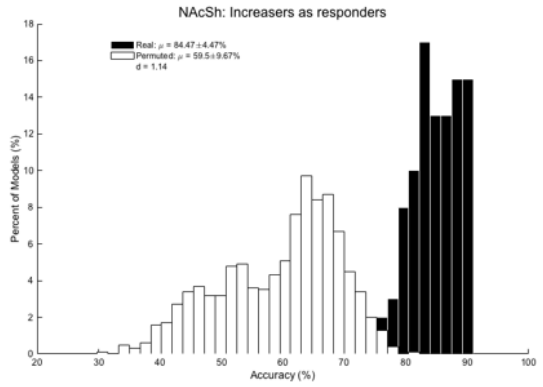
Figure 4. Individual-based prediction models. Corticostriatal circuit activity predicts which rats were increasers or decreasers to NAcSh (**A** and **B**) and mPFC (**C** and **D**) DBS. Baseline levels of alcohol consumption (g/kg) were not meaningfully predicted by corticostriatal circuit activity due to high absolute error (0.4 g/kg; **E**). Summary model of the prediction outcomes (**F**). Corticostriatal circuit activity predicts response to NAcSh and mPFC DBS, but not baseline alcohol consumption. There was a trend ($p=0.09$) for baseline alcohol consumption to predict response to NAcSh (but not mPFC) DBS.


Arrival and acclimation
Electrode implantation and recovery
Alcohol drinking training
NAcSh *or* mPFC DBS during drinking
Washout
NAcSh *or* mPFC DBS during drinking
Baseline LFP recordings

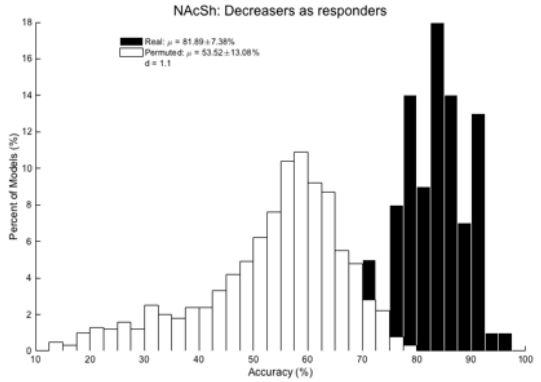

A
NAcSh Responders vs. Nonresponders
Percent Change (%)
Animal
B
+1.6mm
+1.2mm
+0.7mm
C
mPFC Responders vs. Nonresponders
Percent Change (%)
Animal
D
+3.7mm
+3.2mm


A
NAcSh DBS
Mean (+SEM) g/kg of alcohol consumed
0.8
0.6
0.4
0.2
0
Baseline
1
2
3
Session
B
mPFC DBS
Mean (+SEM) g/kg of alcohol consumed
0.8
0.6
0.4
0.2
0
Baseline
1
2
3
Session
C
NAcSh
Mean (+SEM) g/kg of alcohol consumed
1
0.8
0.6
0.4
0.2
0
*
Decreasers
Increasers and Nonresponders
D
mPFC
Mean (+SEM) g/kg of alcohol consumed
1
0.8
0.6
0.4
0.2
0
Decreasers
Increasers and Nonresponders

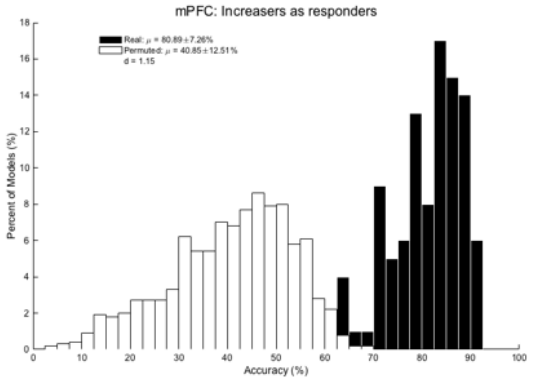
A


NAcSh: Increasers as responders
Real: μ = 84.47±4.47%
Permuted: μ = 59.5±9.67%
d = 1.14
Percent of Models (%)
Accuracy (%)

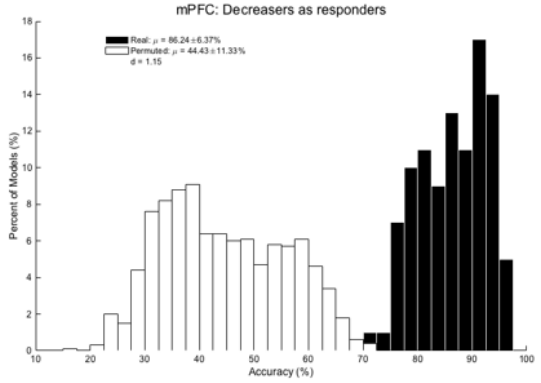
B


NAcSh: Decreasers as responders
Real: μ = 81.89±7.38%
Permuted: μ = 53.52±13.08%
d = 1.1
Percent of Models (%)
Accuracy (%)

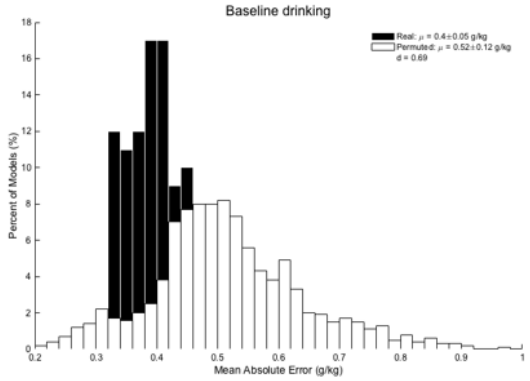
C


mPFC: Increasers as responders
Real: μ = 80.89±7.26%
Permuted: μ = 40.85±12.51%
d = 1.15
Percent of Models (%)
Accuracy (%)

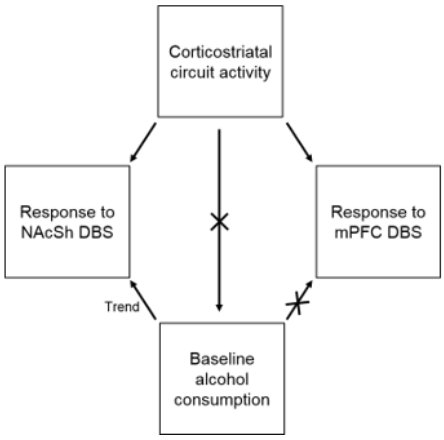
D


mPFC: Decreasers as responders
Real: μ = 86.24±6.37%
Permuted: μ = 44.43±11.33%
d = 1.15
Percent of Models (%)
Accuracy (%)

E


Baseline drinking
Real: μ = 0.4±0.05 g/kg
Permuted: μ = 0.52±0.12 g/kg
d = 0.69
Percent of Models (%)
Mean Absolute Error (g/kg)

F


Corticostriatal circuit activity
Response to NAcSh DBS
Response to mPFC DBS
Trend
Baseline alcohol consumption