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May 22, 2018

To the Members of the Selection Committee:

Application of Lucas Dwiel

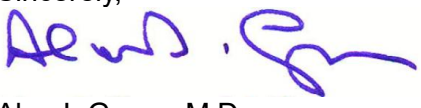
As Lucas Dwiel's primary mentor within the PEMM program, I am delighted to strongly support his application for the Neukom Institute Outstanding Undergraduate Research in Computational Science Prize.

Since his first rotation in my lab, now over two years ago, Lucas has continued to impress me with his devotion to high caliber science and his initiative in seeking out mentors to teach him new methods in signal processing and machine learning. Within the lab, he has worked most directly on a series of studies related binge eating and alcohol drinking; his contributions to these studies have been absolutely crucial to their success. He brought into the lab (or developed once here) analytical skills showcased in a number of our recent manuscripts already under review or soon to be submitted (e.g., Doucette et al., which he has included with his application, as well as Dwiel et al. and Henricks et al. – see below). Working with Drs. van der Meer (from Psychological and Brain Sciences) and Gui (from Biomedical Data Science), he was able to write code for signal processing and machine learning, which he used for the analytic work in these three papers. The first two studied a rat model of binge eating and the last one focused on a rat model of alcohol drinking. In step-wise fashion, the papers reflect the growth of Lucas's analytic strategy and abilities. The first paper identified a series of local field potentials that were able to predict a decrease in eating in an animal in response to localized deep brain stimulation (DBS). The second paper attempted to identify local field potential "signatures" of feeding behavior, and importantly also demonstrated the ability to predict when an animal was about to eat. In the third manuscript, which involved alcohol drinking, Lucas again demonstrated that successful DBS (resulting in decreased drinking) could be predicted by local field potentials recorded from the corticostriatal brain circuit. Combined with his other publications (from his undergraduate research), this body of work is an impressive accomplishment for a third-year graduate student.

Lucas's research studies combining computational methods with translational models of behavior have tremendous importance for the study of psychiatric illnesses. The paper included with his application is a perfect example of how Lucas is applying cutting-edge computation methods to translational neuroscience experiments – paving the way for future clinical investigators interested in developing effective neurostimulation protocols or in understanding the neural underpinnings of behavior.

For these reasons and with the paper he included with his application as an exemplar of the first-rate quality of his computational neuroscience research, I strongly endorse Lucas Dwiel's candidacy for the Neukom Institute Outstanding Undergraduate Research in Computational Science Prize.

Sincerely,



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Page two:

Doucette, W., **Dwiel, L.**, Boyce, J., Simon, A., Khokhar, J., & Green, A. Machine learning based classification of deep brain stimulation outcomes in a rat model of binge eating using ventral striatal oscillations. Under review, *Frontiers in Psychiatry*.

Dwiel, L., Connerney, M., Green, A., Khokhar J., & Doucette, W. An unbiased decoding of ventral striatal oscillations in a rat model of binge eating: Finding the balance between model complexity and performance. To be submitted to *Journal of Neuroscience*.

Henricks, A., **Dwiel, L.**, Deveau, N., Green, A., & Doucette, W. 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. To be submitted to *Translational Psychiatry*.

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May 21, 2018

To whom it may concern,

I am very pleased to hear that Lucas Dwiel is applying for the Neukom Institute Outstanding Undergraduate and Graduate Research in Computational Science Prize.

It is exciting to meet a graduate student who is as motivated as Lucas to correctly apply cutting-edge computational techniques to translational research. Lucas primarily uses the machine learning algorithm lasso to find patterns in the brain activity of rodents that are predictive of treatment outcome and behaviors. The work that Lucas is submitting in consideration for this prize (currently under revision at Frontiers in Neuroscience) utilize this method to predict if a binge-eating rodent would reduce their consumption when treated with deep brain stimulation targeting the reward pathway. Further, he was able to use the same methods to determine which of two brain regions should be stimulated to elicit the largest reduction in consumption. His success in building models to make these predictions using brain activity data is especially exciting given the potential translational role for these methods in humans deciding if they should undergo such an invasive procedure as neurosurgery to implant deep brain stimulators and where should the stimulators target to provide the best chance for successful treatment.

Lucas's goals of applying powerful computational methods for the purposes of predicting treatment response in binge eating also has great potential to be generalized across disorders treated with neuromodulation (e.g., depression, anxiety, substance abuse, and Parkinson's disease). Beyond the impact Lucas's work will have upon translational neuroscience, Lucas has also demonstrated an impressive degree of self-motivation in learning and applying advanced computational methods. Upon his own initiative he sought me out to mentor him in machine learning as well as Dr. van der Meer (Psychological and Brain Sciences) for signal processing. The work submitted here typifies how Lucas has been able to combine both of these complex analytical methods to explore the ability to personalize and improve psychiatric treatment.

I am happy to recommend Lucas for this prize from the Neukom Institute as I believe his drive to utilize cutting-edge computational methods to improve translational research is representative of exactly the kind of graduate student the prize was created for.

Best,

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Title: Machine learning based classification of deep brain stimulation outcomes in a rat model of binge eating using ventral striatal oscillations.

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Abstract

Neuromodulation-based interventions continue to be evaluated across an array of appetitive disorders but broader implementation of these approaches remains limited due to variable treatment outcomes. We hypothesize that individual variation in treatment outcomes may be linked to differences in the networks underlying these disorders. Here, Sprague-Dawley rats received deep brain stimulation separately within each nucleus accumbens (NAc) sub-region (core and shell) using a within-animal crossover design in a rat model of binge eating. Significant reductions in binge size were observed with stimulation of either target but with significant variation in effectiveness across individuals. When features of local field potentials (LFPs) recorded from the NAc were used as predictors of the pre-defined stimulation outcomes (response or non-response) from each rat using a machine-learning approach (lasso), stimulation outcomes could be predicted with greater accuracy than expected by chance (effect sizes: core = 1.13, shell = 1.05). Further, these LFP features could be used to identify the best stimulation target for each animal (core vs. shell) with an effect size = 0.96. These data suggest that individual differences in underlying network activity may contribute to the variable outcomes of circuit based interventions, and measures of network activity have the potential to individually guide the selection of an optimal stimulation target and improve overall treatment response rates.

Introduction

Brain stimulation has demonstrated the potential to improve symptoms in Parkinson's disease, depression and obsessive-compulsive disorder, yet highly variable treatment outcomes (especially common in psychiatric disorders) indicate that the full potential of brain stimulation is not being met (Sturm et al., 2003; Mayberg et al., 2005; Toft et al., 2011). The majority of these studies evaluate the treatment outcomes of a single brain target despite pre-existing evidence supporting the potential of other stimulation targets (Mayberg et al., 2005; Schlaepfer et al., 2008; Ahmari and Dougherty, 2015; Deeb et al., 2016). With these constraints, treatment outcome improvements have mostly been achieved to date through more stringent inclusion/exclusion criteria and improved precision in modulating the intended brain target (Riva-Posse et al., 2014; Smart et al., 2015; Filkowski et al., 2016). Another potential avenue to improve treatment outcomes for a specific disorder could be achieved through the personalization of target selection. This approach was pioneered by cancer biologists who used tumor immunoprofiling to personalize chemotherapy, and it remains unknown if personalization of target selection for neuromodulation-based treatments has a similar potential to improve treatment outcomes in neuropsychiatric diseases including disorders of appetitive behavior.

Clinical studies that used invasive or non-invasive stimulation in disorders of appetitive behavior (e.g., addiction, binge eating and obesity) have demonstrated the potential of targeting an array of different brain areas, but also demonstrated considerable treatment response heterogeneity across individuals (Valencia-Alfonso et al., 2012; Whiting et al., 2013; Deeb et al., 2016; Nangunoori et al., 2016; Terraneo et al., 2016; Spagnolo and Goldman, 2017). The pre-clinical literature on deep brain stimulation (DBS), while also encouraging for appetitive disorders, reveals considerable outcome variation resulting from the targeting of different brain regions across studies. In addition, most studies report only group-based effects, masking the problem of variation across individuals (Luigjes et al., 2012; Guo et al., 2013; Pierce and Vassoler, 2013).

In this study, we used an established rat model of binge eating to produce binge-like feeding behavior (Corwin, 2004; Corwin and Buda-Levin, 2004; Berner et al., 2008). Similar rodent models of binge eating have resulted in weight gain (Berner et al., 2008), compulsive feeding behavior (Oswald et al., 2011; Heal et al., 2016) and increased impulsivity (Vickers et al., 2017) thus displaying traits conceptually similar to those seen in patients with binge eating disorder. It is important to acknowledge, however, that this is a pre-clinical approximation of the clinical condition, and many successful pharmacologic trials using this rodent/rat model have failed to translate clinically with the exception of lisdexamfetamine (Vickers et al., 2015; McElroy et al., 2016). Using this pre-clinical model of binge eating, we have previously shown variation in individual rat outcomes receiving deep brain stimulation targeting the nucleus accumbens core with about 60% of rats displaying a significant reduction in binge size with stimulation (Doucette et al., 2015). When non-invasive, repetitive transcranial magnetic stimulation was targeted to a related area of the reward circuit in patients with binge eating, the frequency of binges decreased in 18 of 28 subjects (~60%) (Dunlop et al., 2015). While the primary outcome in clinical and pre-clinical studies tend to be different (frequency of binges vs. size of binges), this rat model of binge eating could provide insight into the source of stimulation outcome variability and provide a model to explore the potential feasibility and benefit of personalized target selection for stimulation-based interventions.

We theorize that individual variation in brain stimulation outcomes targeting a specific brain region may be linked to individual differences in the networks underpinning the symptom of interest (e.g., binge eating) (Dunlop et al., 2015). It follows that measures of relevant network activity could be used to predict brain stimulation outcomes at a given brain target or could be used to individualize the choice between potentially viable targets. This study was designed to compare the treatment efficacy of stimulation targeted to either the nucleus accumbens (NAc) core or shell, two regions with known differences in anatomical and functional connectivity and different functional roles across an array of reward-related behaviors (Burton et al., 2014;

Haber, 2016). This study replicated our previous treatment outcome variance with NAc core stimulation (Doucette et al., 2015) and extended the results to assess whether similar variation in treatment outcomes occurs with NAc shell stimulation (previously reported by Halpern et al. to be effective in a mouse model of binge eating) (Halpern et al., 2013; Wu et al., 2017). We then determined whether a relationship existed between individual stimulation outcomes and either corresponding performance on reward-related behaviors, local field potential recordings from the NAc sub-regions or variation in electrode localization within each NAc sub-region.

Methods and Materials

Animals and Surgery

Male Sprague-Dawley rats were purchased from Charles River (*Shrewsbury, MA*) at 60 days of age and individually housed using a reverse 12 hour light/dark schedule with house chow and water available *ad libitum*. Following habituation to the animal facility, rats were implanted with a custom electrode array that targeted both the NAc core and shell bilaterally, according to the following coordinates relative to bregma: 1.6 mm anterior; ± 1 and 2.5 mm lateral; and 7.6 mm ventral. Animals were excluded from analysis if later histological examination revealed electrode locations outside the NAc core or shell. All experiments were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised in 1996 and approved by the Institutional Animal Care and Use Committee at Dartmouth College.

Binge Eating Paradigm

Following recovery from surgery (~1 week), rats began a schedule of limited access to a palatable high-fat, high-sugar diet ("sweet-fat diet"), which contained 19% protein, 36.2% carbohydrates, and 44.8% fat by calories and 4.6 kcal/g (Teklad Diets 06415, *South Easton, MA*) as previously described (Berner et al., 2008). The sweet-fat diet was provided to the rats in addition to house chow and water within stimulation chambers for 2 hour sessions during 4-5 sessions per week (irregular schedule). Following 16-20 sessions, the rats were consuming a

stable and significant amount of sweet-fat food during each session (mean = 54% of their daily caloric intake ± 12% [1 standard deviation]). This “binge-like” feeding has been shown to result in more significant weight gain than was observed with continuous access to the same diet -- as is used in models of diet-induced obesity (Berner et al., 2008). Prior work has also demonstrated that chronic, irregular, limited access to palatable food can result in compulsive feeding behavior(Oswald et al., 2011;Heal et al., 2016) and increased impulsivity (Vickers et al., 2017). Palatable sweet-fat and regular house chow consumption were measured during all limited access sessions.

Stimulation

To deliver stimulation, a current-controlled stimulator (*PlexStim, Plexon, Plano, TX*) was used to generate a continuous train of biphasic pulses. 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 animals had access to the sweet-fat food and turned off at the completion of the 2 hour session.

Overall Design

Experiment 1 (N=8 rats) was used to determine the optimal stimulation parameters to reduce binge size using our custom electrode arrays targeting the NAc core or shell. Experiment 2 (N=9) used a crossover design in a separate cohort of rats to test DBS targeting the NAc core or shell with the optimized stimulation parameters identified in Experiment 1. Last, rats from Experiment 1 and 2 that had received the optimized stimulation parameters in both NAc targets and remained in good health (N=12) continued on to Experiment 3 and underwent behavioral and electrophysiological characterization (Figure 1A).

Experiment 1 - Identifying optimal stimulation parameters

To identify the optimal stimulation parameters to alter feeding behavior, we tested an array of published stimulation intensities (range: 150 to 500 μA) and electrode contact

configurations (monopolar vs. bipolar using our custom arrays within the targeted brain structures (NAc core and shell). These permutations alter the size and shape of the electric field and the resulting effect that stimulation has on binge eating. Thus, custom electrodes were implanted in the NAc core and shell bilaterally in a cohort of rats (N=8). Rats were randomly divided into two groups for a crossover design with different initial stimulation targets (core or shell). Animals were then trained in the binge eating paradigm until a stable baseline of sweet-fat food intake was established (15-20 sessions over 3-4 weeks) before DBS sessions were initiated. Stimulation current was increased during each subsequent session, starting at 150 μA and progressing to 500 μA in a bipolar configuration (between two wires within the target, separated by ~1mm in the dorsal-ventral plane), and then from 150 μA to 300 μA in a monopolar configuration (between one wire in the target and a skull screw over lambda). The rats then entered a period without DBS in which the effect of prior stimulation was allowed to washout before crossing over to DBS treatment of the other site. Following the washout and a return to baseline, we resumed stimulation in the other NAc target and the same titration of stimulation parameters was repeated at the second target of DBS across multiple sessions (Figure 1A).

Experiment 2 - Testing NAc core vs. shell stimulation using fixed stimulation parameters

Experiment 1 was designed to identify stimulation parameters that were similarly effective in either the NAc core or shell--bipolar stimulation at 300 μA or monopolar stimulation at 200 μA. We elected to use monopolar stimulation (biphasic, 90 μsec pulse width, 130 Hz, 200 μA) as it produced a lower charge density at the electrode surface, which decreases the probability of neuronal injury (Kuncel and Grill, 2004). In a new cohort of rats, (N=9) electrodes were implanted and rats were randomized to receive initial stimulation in either the NAc core or shell. After a stable baseline of sweet-fat diet consumption was established during limited access sessions (following 15-20 sessions), rats received 3 sessions of stimulation followed by

3 sham post-stimulation sessions. Animals then entered a **2 week washout phase** to re-establish baseline prior to crossover and stimulation in the other target (Figure 1A)**.**

Data Analysis

Experiment 1 data analysis

In order to evaluate the effect of DBS in Experiment 1, we defined a meaningful DBS response as any change in consumption that exceeded 2 standard deviations of baseline consumption. To calculate the standard deviation of consumption, we pooled baseline binge eating data from multiple cohorts to characterize variation in baseline binge size within the population (36 rats, 3 baseline sessions per rat, 108 total baseline observations). The data came from all of the animals in this study, a previously published study (Doucette et al., 2015), and unpublished data. Each observation was recorded as the percent change from that rats average baseline binge size. This "normalized variance" was done to account for the known variation between animals in their average binge size at baseline. This session to session normalized variation in binge size was found to be normally distributed, centered at 0% change with a standard deviation of 13% (Figure 1B). Thus, for Experiment 1, if an animal's binge size during a stimulation session was greater or less than 26% (2 standard deviations) of its average baseline binge size it was considered a meaningful change induced by stimulation.

Experiment 2 data analysis

Group-based analysis

We used repeated measures analysis of variance (RMANOVA) and included 3 sessions of baseline, stimulation and post-stimulation data from each animal. Each stimulation target was analyzed independently, as there were no significant differences in binge size between the baseline periods on either side of the crossover. Session number (1-3) and session type (baseline, stimulation, and post-stimulation) were assumed to be categorical variables. When the analysis indicated that differences existed between session types, post-hoc pair-wise

comparisons between groups were made using the Bonferroni method to correct for multiple comparisons.

Individual-based analysis

The presence or absence of a response to stimulation was correlated with reward-related behavior and electrophysiological recordings in each animal. Individual rats were classified as either non-responders [NR] or responders [R] to stimulation at each target based on the criteria used in Experiment 1 (greater than a 2 SD or 26% change in binge size from each animal's baseline average) and this change had to be observed in all three stimulation sessions for a given target.

Experiment 3 - Behavioral and electrical characterization (without stimulation)

All rats from Experiment 2 (N=9) and those rats from Experiment 1 tested with the stimulation parameters chosen for Experiment 2 in both targets (N=3) were included in Experiment 3 (N=12). These animals underwent subsequent behavioral and electrophysiological characterization starting two weeks after the conclusion of Experiment 1 or 2. All rats underwent behavioral testing followed by another 2 week washout and then electrophysiological characterization of each stimulation site, but **all without stimulation** (Figure 1A).

Reward-related behavior (order of testing)

To determine if variation in reward-related behavior could capture the underlying network differences that may be responsible for the variation in DBS outcomes, 3 reward-related behaviors were assessed. Behavioral outcomes were compared between NR and R groups for each DBS target using a two-way t-test. A significance threshold of $p<0.05$ was used to screen for behaviors with a potential relationship with stimulation outcomes.

Increased sweet-fat diet intake with food deprivation (1)

Food deprivation (24 hours) was used to push the energy homeostasis system towards an orexigenic state. Individual variation in the resultant changes in binge size from baseline was

231 measured. Thus, the primary outcome was the percent change in binge size from each rat's
232 baseline average to that observed following food deprivation.
233 Locomotor response to novelty (2)
234 Locomotor response to novelty was chosen because of previous correlations between
235 variation in this behavior (high and low responders) and a sensation-seeking behavioral
236 phenotype linked to a higher risk for developing disorders of appetitive behavior (Piazza et al.,
237 1989;Belin et al., 2008). Briefly, rats were placed in a 1.5 ft X 3 ft black plastic chamber that was
238 novel to the animal and allowed to freely explore for 50 minutes while video was recorded.
239 Video files were analyzed offline using automated contrast-based tracking (Cineplex software,
240 *Plexon, Plano, TX)* to calculate the distance traveled (primary outcome).
241 Conditioned place preference (CPP) (3)
242 CPP was assessed due to the known involvement of the NAc in CPP (Tzschentke,
243 2007). We used an established 2-chamber biased design paradigm, pairing the sweet-fat food
244 with the individual animal's non-preferred chamber and regular house chow with the preferred
245 chamber (30 minute pairing, 1 pairing per day, alternating between the 2 chambers for 4 days)
246 (Calcagnetti and Schechter, 1993; Valjent et al., 2006). Baseline and test sessions (15 minutes)
247 were video recorded and automatically scored using contrast-based tracking to assess time
248 spent in each chamber. The primary outcome was the change in the percentage of time spent in
249 the initially non-preferred chamber (paired with sweet-fat diet).
250 *Local field potential (LFP) recording*
251 We recorded local field potential (LFP) activity bilaterally from the NAc core and shell of
252 each animal to assess whether variation of intrinsic network characteristics in the absence of
253 stimulation could predict stimulation outcomes. Rats were tethered in a neutral chamber through
254 a commutator to a Plexon data acquisition system while time-synchronized video images were
255 recorded (*Plexon, Plano, Tx*) for offline analysis. Using the video images, rest intervals were
256 manually identified as extended periods of inactivity, and only recordings from these intervals

were used in the analysis. We used well-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 NAc core and shell) for each animal using custom code written using Matlab R2015b (Cohen et al., 2009; McCracken and Grace, 2009; Catanese et al., 2016) (Supplemental Methods). Each rat recording session produced 60 LFP features: 24 measures of power (6 frequency bands X 4 brain locations) and 36 measures of coherence (6 frequency bands X 6 possible location pairs, Figure 5A and B). **We obtained two recordings from each animal that were separated in time by between 2 and 71 days to control for potential day to day variation in LFPs.**

Linking ventral striatal activity to stimulation outcomes

As there were many more predictor variables than number of animals, we employed a machine learning approach to determine if there was information within the LFP signals that correlated with stimulation outcomes. We used a penalized regression method, lasso, to reduce the dimensionality of the predictor variable set by removing LFP features that contained no information or redundant information and extracted the smallest combination of LFP features that most accurately described the observed variation in stimulation outcomes. The Matlab package *Glmnet* was used to implement the lasso using a 4-fold cross-validation scheme with 100 repetitions for each model (Core R vs. NR, Shell R vs. NR, and Core vs. Shell). For the Core vs. Shell model, each animal's optimal stimulation target was defined as the stimulation target that produced the largest average reduction in binge size (rats without a significant reduction were excluded). The accuracy of the models is reported as the average cross-validated accuracy. In order to determine if the achieved accuracies were meaningfully better then chance, the entire process described above was repeated for ten random permutations of the data for each model type. The permutations randomized the relationship between the binary stimulation outcomes (R=1, NR=0) or optimal target assignment (Core =1, Shell=0) with the individual rat LFP feature sets to maintain the overall structure of the data, but permute the

relationship of dependent to independent variables. The distribution of accuracies from the observed data was compared to the distribution from the permuted data using the Mann-Whitney U test, and the U test statistic was converted into a Cohen's d effect size.

If the lasso indicated that information existed in the LFP signal, a subsequent investigation of each LFP feature was carried out to determine which features contained the most information. For this, logistic regressions were implemented using the Matlab function *fitglm* to build models to classify: 1) core responses; 2) shell responses; or 3) core or shell as the best stimulation target for each animal. For the logistic models, an exhaustive leave-one-out, cross-validation was used to obtain a distribution of accuracies, and the mean accuracy from these distributions is reported in Table 1 for the top 5 LFP features from each model type.

Verification of electrode placement

At the conclusion of all experiments, rats were euthanized, and the brains were removed, prepared for cryostat sectioning, mounted slides, and stained (thionine) for histological analysis of electrode placement (Doucette et al., 2015). All animals included in the results had electrodes located within the target structure (Figure 4C).

Results

Experiment 1 - Identifying optimal stimulation parameters

Figure 2A summarizes the outcome of stimulation in the NAc core; significant reductions in food intake were observed with a bipolar configuration (300 μA) in 3/8 animals and with monopolar configuration (200-300 μA) in 4/8 animals. Figure 2B summarizes the outcomes of stimulation of the NAc shell in which significant reductions in food intake were observed in a subset of animals that received bipolar and monopolar stimulation. Interestingly, a subset of the shell-stimulated animals had significant increases in food intake at higher stimulation intensities. An example of an individual rat's food intake across tested stimulation parameters in the NAc core and shell is shown in Figure 2C. There were significant reductions in food intake during stimulation in the NAc shell at bipolar 300 μA and monopolar 200 μA with no significant food

intake changes with core stimulation (shell only). Figure 2D illustrates the entire cohort's individual response profiles.

As demonstrated by the example rat, many animals responded to stimulation in only one of the two NAc sub-regions, despite testing across a range of stimulation parameters. Overall, this cohort of animals helped us identify a stimulation configuration (*[monopolar]* and parameters *[130 Hz, 90 μsec pulse width, and 200 μA]*) for the custom arrays that was capable of decreasing food intake when targeting either the NAc core or shell.

Experiment 2 - Testing NAc core vs. shell stimulation using optimized stimulation parameters

Figure 3A shows the population outcomes for this cohort (N=9). Using standard population statistics (RMANOVA), a main effect for session type (baseline, stimulation, post-stimulation) was observed in the shell stimulation set ($F(1,8) = 8.171$, $P = 0.02$) and in the core stimulation set ($F(1,7) = 3.772$, $P = 0.05$). In order to determine which sessions were different, post-hoc pairwise comparisons with Bonferroni adjustment showed a significant difference between the baseline sessions and each stimulation session ($p<0.05$), but not between the baseline sessions and the post-stimulation sessions.

To determine which rats responded to NAc core and shell stimulation, our *a priori* definition of responders and non-responders was used. The individual responses to NAc core and shell stimulation are shown in Figure 3B and C respectively, with significant individual responders shown in black and non-responders shown in grey. In this cohort, 5/9 rats responded to shell stimulation, 4/9 rats responded to core stimulation, and 5/9 rats responded to stimulation in only one of the two targets. Overall (Experiment 1 and 2), 10/17 rats (~60%) responded to only one of the two stimulation targets highlighting the need for individualized targeting.

Experiment 3 - Behavioral and electrical characterization (without stimulation)

Relationship between stimulation outcomes and reward-related behavior

It was our hypothesis that innate variation in NAc core and shell networks would be a common source of variation in reward-related behavior and stimulation outcomes. Thus, we expected to see a relationship between variation in reward-related tasks and stimulation outcomes. The behavioral metrics of the 12 rats studied were grouped based on the rat's individual response to stimulation as defined previously (R - responder and NR - non-responder for each stimulation target), differences between R and NR groups were evaluated with t-tests. None of the behavioral measures differed as a function of the R/NR grouping for either stimulation site, core- (Figure 4A) or shell- (Figure 4B).

Relationship between stimulation outcomes and electrode localization

Figure 4C-E illustrates the relationship of anterior-posterior (A-P) position in the core (Figure 4D) and the shell (Figure 4E) and the corresponding stimulation outcomes (black -- responders; grey -- non-responders). Variation of electrode location within the A-P dimension displayed no discernable relationship with stimulation outcomes.

Relationship between stimulation outcomes and local field potential activity

The lasso used information contained within LFP features, existing at the stimulation sites when stimulation was not present, to determine which response group an animal belonged to with an average accuracy for core stimulation of 72% (standard deviation ± 5%), outperforming the models produced from random permutations of the data (49% accuracy ± 11%) with an effect size of 1.13 (Figure 5C). The lasso models classifying shell stimulation outcomes performed with an average accuracy of 65% (standard deviation ± 7%), outperforming the models produced from random permutations of the data (49% accuracy ± 11%) with an effect size of 1.05 (Figure 5E). Finally, each rat with a significant reduction in binge size was grouped by the target (NAc core or shell) that produced the largest average reduction in binge size across the three stimulation sessions. LFP features were able to match

individual rats to the most effective target for stimulation using lasso with an average accuracy of 76% (standard deviation ± 7%) compared to 59% (standard deviation ± 8%) for the permuted data with an effect size of 0.96 (Figure 5D).

It is important to note that each rat had 2 LFP recording sessions separated by up to 70 days, and each recording session was separately incorporated into the model. Therefore, only LFP features that had stable differences between groups (e.g., R vs. NR) across time were selected and used by lasso. An example of one of the selected LFP features is shown in Figure 5F, which indicates that the feature varied less between day 1 and day 71 within each animal than it did between the responder and non-responder groups (Figure 5F -- black horizontal lines). This finding indicates that the information about stimulation outcomes extracted from LFP signals was stable through time.

To determine which components of the LFP signal contained the most information about stimulation outcomes, each feature's performance in logistic models (% accuracy) was compared to how commonly those features were included in the (lasso) models (% survival). Table 1 lists the top 5 LFP features from the logistic and lasso models of core and shell stimulation outcomes (R vs. NR) and the classification of the optimal target for each animal (core vs. shell). This exploration revealed a predominance of delta band features in the logistic models that did not translate to survival in the lasso models suggesting that while delta features contained the most information about outcomes, this information was likely highly redundant. Thus, only one delta feature tended to be included in the lasso models. Arrows in the table indicate the directionality of the feature differences between groups.

Discussion

These experiments demonstrate that deep brain stimulation of either the nucleus accumbens core or shell, regions with known differences in brain connectivity and distinct functional roles in appetitive behaviors, have a similar capacity to reduce "binge-like" feeding behavior. Experiment 1 demonstrated that despite titration across multiple stimulation

parameters only subsets of animals showed significant changes in binge behavior with stimulation in either of the tested targets. Experiment 2 confirmed this finding and an evaluation of individual responses across the first two experiments illustrated that 66% of rats respond to DBS in only one of the two targets, supporting the likelihood that personalized target selection could improve treatment outcomes. Experiment 3 demonstrated that variation in stimulation outcomes could be, in part, explained by individual differences in recorded local field potential activity in the absence of stimulation using a machine learning-based approach (lasso). This implies that activity from the network underlying appetitive behavior could determine the likelihood that a given individual will achieve a meaningful suppression of binge eating with stimulation. Most importantly, ventral striatal oscillations were also capable of classifying the most effective stimulation target for each individual, demonstrating the feasibility of using network activity under baseline, unstimulated conditions to personalize target selection for neuromodulation-based treatments. However, it must be noted that these recordings and predictions were done post hoc, therefore it would be fruitful to verify these results in future work in which the recordings and predictions are conducted before stimulation. Our results suggest that such studies would be successful.

The translational relevance of this work is supported by previously observed treatment outcome variability in clinical studies of focal stimulation in disorders of appetitive behavior (Deeb et al., 2016; Terraneo et al., 2016; Azevedo and Mammis, 2017). As an example, in a study using repetitive transcranial magnetic stimulation of the medial prefrontal cortex for patients with binge eating, differences in cortical-striatal network activity were shown to correlate with responses to stimulation (Dunlop et al., 2015). Therefore, it is notable in this study that a large proportion of animals that failed to respond to stimulation in one brain target (NAc shell), responded to stimulation in an alternative target (NAc core). Further, results from this study suggest that network activity recorded without stimulation in the ventral striatum contains information that can predict the optimal target for stimulation on an individual basis. This finding

411 suggests that even in this outbred rat model of binge eating, there are likely individual
412 differences in the networks perpetuating the behavioral expression of binge eating.
413 The assertion that variation exists across individuals in the specific cortical-striatal
414 networks that underpin the expression of appetitive behavior is supported by a rich literature
415 including the well characterized spectrum of goal-directed to habitual behavior (Balleine and
416 O'Doherty, 2010; Robinson et al., 2014; Heilbronner et al., 2016; Voon et al., 2017). Thus, the
417 striatal sub-regions driving binge-like behavior could vary across individuals and impact which
418 striatal target (NAc shell vs. core) is most likely to modulate binge behavior. Patients with binge
419 eating have also been shown to display altered function in distinct networks including the
420 reward/salience network (Svaldi et al., 2010; Michaelides et al., 2012; Balodis et al., 2013)
421 and/or the cortical control network (Schienle et al., 2009; Tammela et al., 2010; Hege et al.,
422 2015; Imperatori et al., 2015) using non-invasive methods to assess network activity. Altered
423 function of one of these networks may be enough to perpetuate binge eating (Dunlop et al.,
424 2016), and our work in rats suggests that even within the ventral striatum, different sub-circuits
425 (involving the NAc core or shell) may be underlying the perpetuation of binge eating across
426 individuals. Both clinical and pre-clinical studies suggest that a single stimulation target may not
427 have the capacity to reduce binge eating across all individuals, and our results suggest that
428 measures of relevant network activity could guide the selection of an effective stimulation target
429 for each individual.
430 To translate personalized targeting of neuromodulation-based treatments to patients, the
431 relevant network activity would have to be measured prior to the intervention. This could be
432 accomplished with the use of intracranial electrodes as is done prior to surgery for epilepsy or
433 using a non-invasive approach (e.g., MRI-based). Thus, it is important to consider the
434 relationship between information extracted from LFP oscillations recorded from depth electrodes
435 reported in this study and non-invasive methods of measuring related network activity in
436 patients. Our data suggest that inter-hemispheric coherence at low frequencies (delta and theta)

may be a rich source of information about DBS outcomes. Previous work has established that correlation exists between these LFP features and fMRI derived measures, including resting state functional connectivity (Wang et al., 2012; Murta et al., 2015; Jaime et al., 2017). The work presented in this study supports the inclusion of the ventral striatum and interconnected cortical regions for future investigations that attempt to use brain activity to guide targeting of focal stimulation for binge eating and related disorders of appetitive behavior.

Overall this study was limited by the scope of information used (recordings from bilateral NAc core and shell when stimulation was not present) to build our predictive models. Thus, increasing the number of recording sites to include additional regions in the distributed feeding circuit (e.g., hypothalamic/brainstem, medial prefrontal and orbitofrontal cortex) would be important for future studies, though this may require placement of intracranial electrodes, as is done for planning epilepsy surgery. In particular, recording from cortical regions would have translational relevance to non-invasive clinical measures of brain activity (e.g., EEG) in addition to MRI derived features. Further, although it is possible that models using brain activity during the feeding behavior rather than rest would perform better, collecting brain data during binge eating in patients is much less feasible than collecting resting state data. Future studies will incorporate pre-stimulation recordings in order to capture network dynamics in treatment naïve animals. In addition, although using penalized regression (lasso) mitigated the problem of having many more predictor variables than observations, a larger sample size would allow testing of the tuned multivariate regressions on naïve datasets and provide more power to relate variation in electrode location with stimulation outcomes. We cannot rule out the possibility that variation in targeting within the NAc sub-regions also contributed to stimulation outcome variation. Inclusion of a female cohort would have increased the generalizability of this study as more women suffer from binge eating compared to men. Last, none of the reward-related behaviors tested in this study showed the potential to predict stimulation outcomes, suggesting that the network dynamics within the NAc that determine the response to DBS differ significantly

from the network elements driving variation in the tested behaviors. However, it is possible that alternative reward-related behaviors may better capture the individual variation that underlies the variation in stimulation outcomes (Robinson et al., 2014; Singer et al., 2016).

Conclusion

For the treatment of many psychiatric disorders, as demonstrated here in a rat model of binge eating, a single target for neuromodulation-based treatment may not be effective across all individuals. Rather, an individualized treatment approach that uses network activity to guide the personalization of target selection could reduce current treatment outcome variability.

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Figure Legends

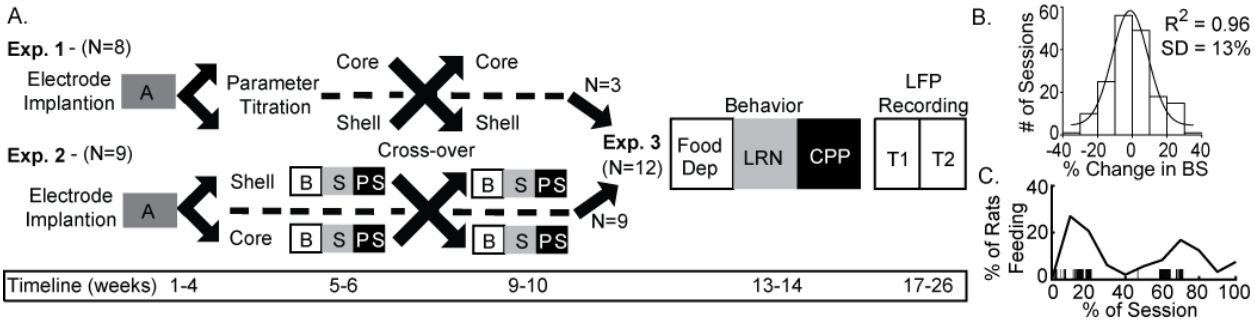


Figure 1. Experimental design and timeline with population data used to define significant change in binge size from baseline. **A.** Experimental design for Experiments 1-3 with timeline shown at bottom. A - acquisition of stable binge size following chronic irregular limited access and randomization to initial stimulation target, B - baseline sessions, S - stimulation sessions, PS - post-stimulation sessions, Food Dep - food deprived binge session, LRN - locomotor response to novelty, CPP - conditioned place preference, LFP Recording - local field potential recording at two time points (T1 and T2). **B.** Population baseline data (3 sessions per animal, N=36 animals) was used to determine an *a priori* definition of a significant change from baseline binge size (BS). Distribution of binge size variance across baseline sessions was fit to a normal distribution with R^2 fit shown (1 standard deviation [SD] = 13% change from baseline average). **C.** The percentage of animals engaged in feeding behavior through a normalized binge session had a bimodal distribution. Vertical black lines under the curve provide an individual example of all of the feeding epochs from a single animal through a binge session.

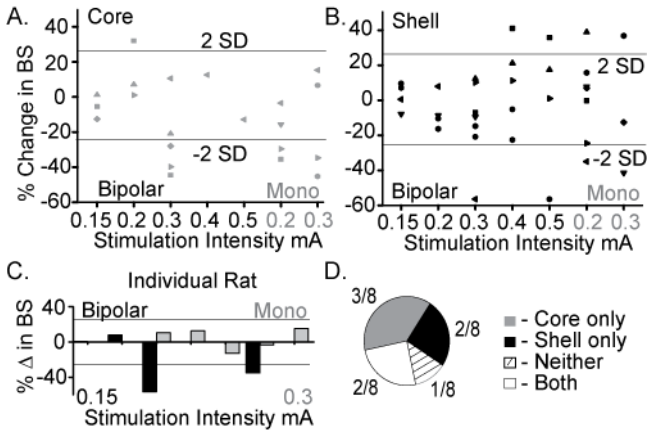


Figure 2. Optimal stimulation parameters were identified that could reduce binge size (BS) using the electrode arrays targeting the NAc core and shell. **A.** Titration of stimulation parameters in NAc core reveals bipolar 300μA and monopolar 200μA are both effective and roughly equivalent. Bipolar (black) and monopolar (Mono, grey) stimulation configurations with corresponding current intensities shown on x-axis. **B.** Titration of stimulation parameters in NAc shell showing similar effective parameters. **C.** Example of a single rat's stimulation response profile illustrating a shell only responder (core - grey; shell - black). Horizontal lines illustrate ± 2 standard deviations (± 26%). **D.** Distribution of stimulation response profiles for this cohort showing that 5/8 animals responded to only one of the two stimulation targets.

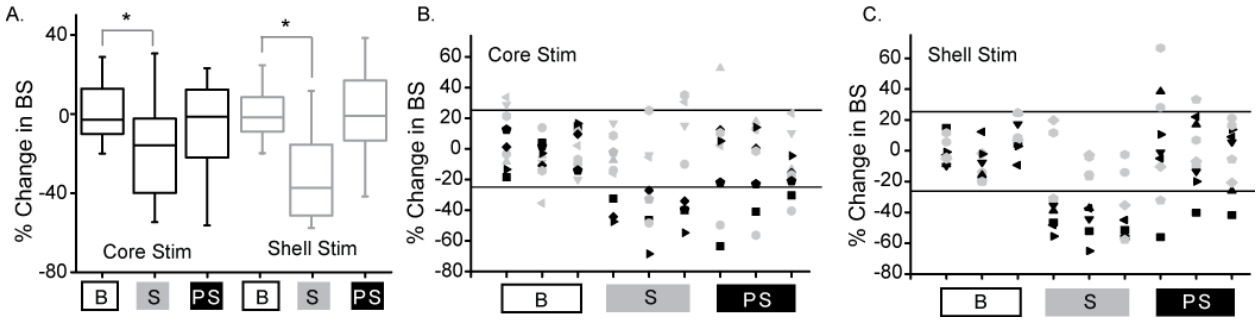


Figure 3. Deep brain stimulation targeted to either the NAc core or shell produces significant reductions in binge size using group-based analysis but with clear individual responders and non-responders. **A.** Group-based analysis (RMANOVA) with post-hoc evaluation revealed a significant difference between baseline (B) and stimulation (S) sessions but not between

baseline and post-stimulation (PS) sessions with either core (black) or shell (grey) targeted stimulation (* p 0.05, boxplots - 95% CI). **B.** Individual rat responses to core stimulation with responders (black, 4/9) and non-responders (grey, 5/9). Horizontal lines illustrate ± 2 standard deviations (± 26%). **C.** Individual rat responses to shell stimulation with responders (black, 5/9) and non-responders (grey, 4/9).

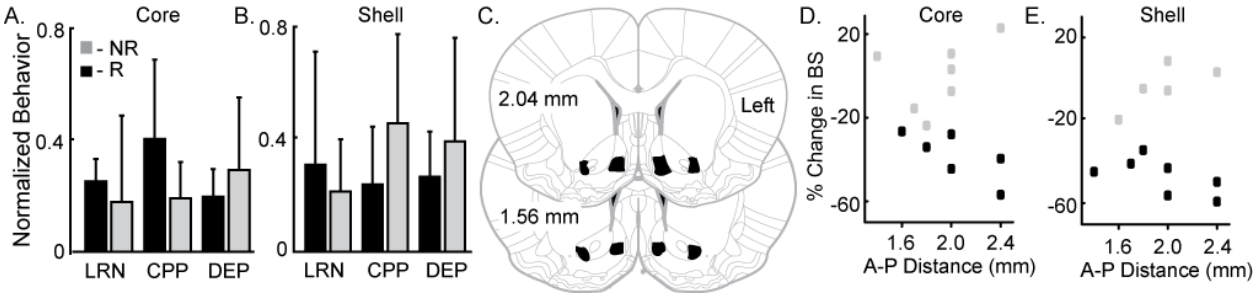
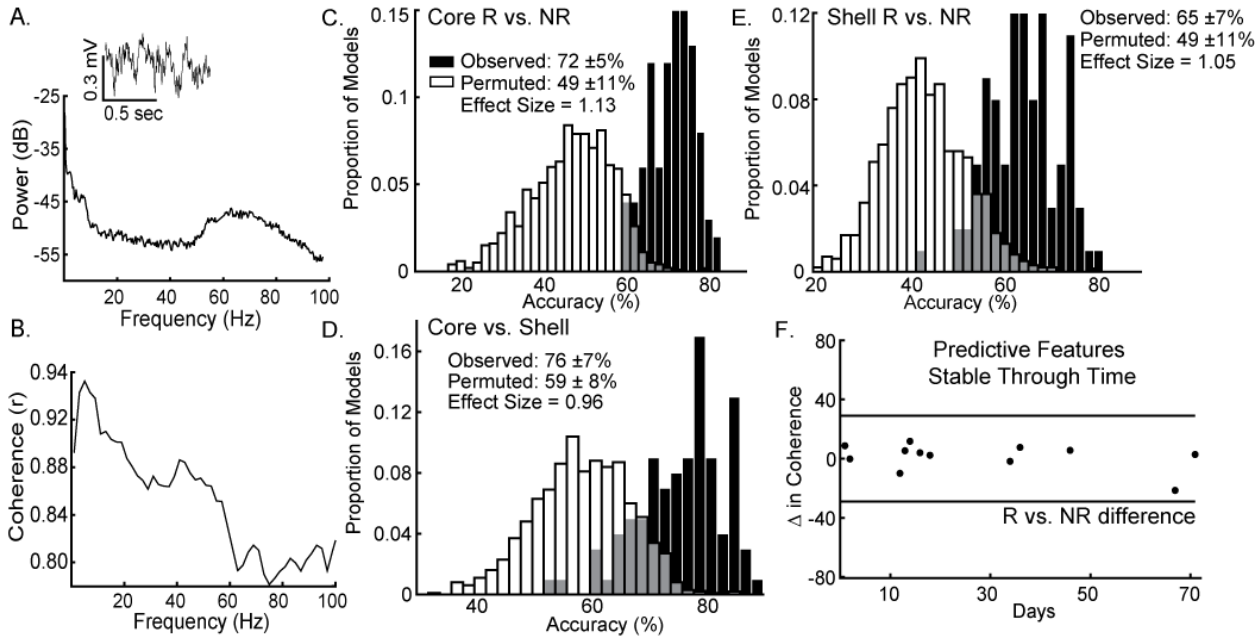


Figure 4. Variation in reward-related behavior and electrode location does not relate to stimulation outcomes. Normalized behavioral data grouped by core (**A**) and shell (**B**) DBS response type --responders (R; black) and non-responders (NR; grey). No significant differences were observed between R and NR groups for the following outcomes: 1) total distance travelled during locomotor response to novelty (LRN); 2) change in the percent of time spent in the initially non-preferred chamber during conditioned place preference (CPP); and 3) percentage increase in food intake after 24 hours of food deprivation (DEP). **C.** All rats included in the analysis had electrode locations within the bilateral NAc core and shell with electrodes localized within the black shapes collapsed onto two representative coronal sections. The largest variation in electrode positioning occurred along the anterior-posterior (A-P) dimension (1.4 to 2.4 mm anterior to bregma). No discernable relationship between electrode placement along the A-P axis in NAc core (**D**) or shell (**E**) corresponded to stimulation outcomes -- responder (black) or non-responder (grey).



720

721 **Figure 5.** Local field potential (LFP) features recorded from ventral striatum can classify
722 individual stimulation outcomes and are stable through time. **A.** Inset of a raw LFP trace from
723 the left NAc core with its corresponding power spectral density plot. **B.** Corresponding
724 coherence plot showing phase relationships across frequencies between the left NAc shell and
725 right NAc core. The distribution of accuracies from classifying NAc core (**C**) and shell (**E**)
726 stimulation responders (R) from non-responders (NR) using the observed data (black) and the
727 permuted data (white) with mean accuracy ± standard deviation listed for each distribution.
728 Effect sizes between observed and permuted distributions are also shown. **D.** Distribution of
729 accuracies classifying the optimal target for stimulation (core vs. shell) for each animal using the
730 observed data (black) or the permuted data (white). **F.** The difference in delta coherence
731 (between the left NAc core and right NAc shell) from recording day T1 to T2 (up to 71 days
732 apart) was smaller than the difference observed between the groups of animals that
733 preferentially responded to core or shell.

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Table 1. Top 5 LFP Features for Each Model Type

	Logistic			Lasso		
Core		Features	% Accuracy	R	Features	% Survival
	⬆	C_{SLCL} Δ	0.81	⬆	C_{CLCR} hγ	98
	⬆	C_{SLCR} Δ	0.76	⬇	C_{CLCR} lγ	88
	⬆	P_{SR} Δ	0.70	⬆	C_{CLSR} θ	86
	⬆	C_{CLCR} hγ	0.70	⬇	P_{SL} Δ	76
	⬇	C_{CLCR} Δ	0.68	⬇	P_{SR} θ	74
Shell	⬇	C_{CLCR} Δ	0.73	⬆	P_{CR} Δ	86
	⬆	P_{CR} Δ	0.71	⬇	C_{SLSR} θ	85
	⬇	C_{CLSR} Δ	0.70	⬇	P_{CR} α	81
	⬇	C_{SLSR} θ	0.70	⬆	P_{SL} β	58
	⬆	C_{SLCL} lγ	0.68	⬆	C_{CLCR} β	53
Core vs. Shell	⬆	C_{CLCR} hγ	0.79	⬆	C_{CLSR} Δ	60
	⬇	P_{CR} Δ	0.78	⬆	C_{SLSR} θ	55
	⬇	C_{CLCR} β	0.77	⬇	P_{SL} θ	51
	⬆	C_{CLCR} Δ	0.76	⬇	P_{CR} Δ	49
	⬆	C_{SRCR} θ	0.75	⬆	C_{SLSR} lγ	12

Table 1. The top 5 local field potential features used in single predictor (logistic) and multi-predictor (lasso) models of NAc core and shell stimulation outcomes. Features are described by location (Core Left -CL, Core Right -CR, Shell Left -SL, and Shell Right -SR) and frequency band (delta -Δ, theta -θ, alpha -α, beta -β, low gamma -lγ, and high gamma -hγ). Power features

743 are represented with location and frequency band (e.g., PSR Δ) and coherence features are
744 represented with location pairs and frequency band (e.g., CSLCL Δ). Logistic features were
745 ranked by the average % accuracy of the single variable logistic model using leave one out
746 cross-validation. Lasso features were ranked by how frequently they were used in the lasso
747 models from 100 iterations of cross-validation (% survival). The top five features that were
748 common across logistic and lasso models for a given classification type (e.g., core response [R]
749 vs. non-response) are highlighted in grey. Arrows to the left of the LFP feature indicate whether
750 higher (up) or lower (down) LFP feature values increased the probability of a DBS response (R),
751 or in the Core vs. Shell model the direction that increased the likelihood that Core is the better
752 target for that animal.
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