Characterizing Motor and Cognitive Effects Associated With Deep Brain Stimulation in the GPi of Hemi-Parkinsonian Rats

Samantha R. Summerson, *Member, IEEE*, Behnaam Aazhang, *Fellow, IEEE*, and Caleb T. Kemere, *Member, IEEE*

***Abstract*—The globus pallidus internus (GPi) is the main output nucleus of the basal ganglia, which is associated with a variety of functions including motor performance and cognition. The GPi is one of the primary targets of deep brain stimulation (DBS) in patients with movement disorders. However, the therapeutic mechanism of GPi-DBS is poorly understood and rodent models have not been characterized. Cognitive side effects, such as impulsivity and depression, of DBS treatment for Parkinson's disease are known, but their relationship to the efficacy of the treatment is not well explained. The goal of this study is to illuminate the effects of GPi-DBS on both motor and cognitive function in a hemi-Parkinsonian rat model. In this work, we study the motor performance of the rodents in multiple behaviors, as well as of impulsivity and depression, and consider the relationship between these behavioral variables and the stimulation frequency of the DBS signal. For the first time, the connection is directly established between stimulating the GPi, motor performance and cognition is directly established in the hemi-Parkinsonian rodent model.**

***Index Terms*—Biomedical engineering, biotechnology, brain stimulation, electrical stimulation.**

I. Introduction

PARKINSON'S disease (PD) is a neurodegenerative motor disorder which stems from dysfunction in the basal ganglia (BG) following the cell loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). When the symptoms become pharmacologically intractable, deep brain stimulation (DBS) is a possible alternative treatment. Electrodes are implanted in the brain, unilaterally or bilaterally, in deep brain nuclei; the two main targets for the electrodes are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). These targets and the major pathways within the BG are depicted in Fig. 1. Note that the primate GPi homolog in the rat is the entopeduncular nucleus (EP), which has similar connections within and projecting out of the basal ganglia [1], and in this paper it is understood that GPi in the rodent model refers to the EP.

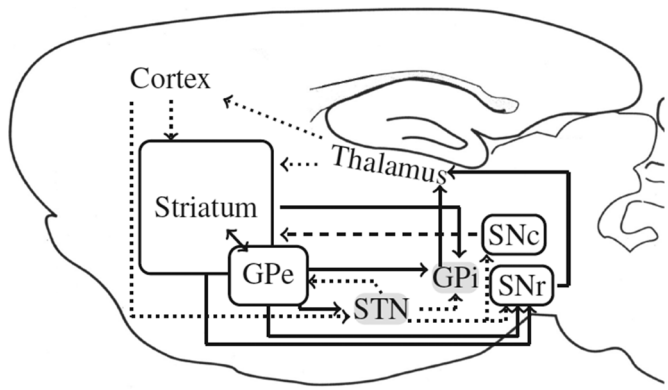


Fig. 1. Major pathways within the basal ganglia, and the pathways for the main input and output nuclei for the basal ganglia. GABAergic pathways (inhibitory) are shown with solid lines and the glutamatergic pathways (excitatory) are with dotted lines. Dopaminergic projection from the SNc to the striatum is depicted with a dashed line. Marked with gray shading are the two main target nuclei, GPi (also known as the entopeduncular nucleus in the rat brain) and STN, for DBS to treat the motor symptoms of PD.

Loss of dopamine in the SNc causes pathological changes in BG neural activity that are related to the symptoms of PD and DBS aims to modulate the activity in order to alleviate some of these symptoms. Although stimulation of both targets, STN and GPi, has been shown to provide therapeutic benefits in human patients [2]–[8], there remains a deficient mechanistic comprehension of DBS. Consequently, optimizing stimulation patterns for DBS in order to maximize therapeutic benefits is challenging. The 6-hydroxydopamine (6-OHDA) rodent model has frequently been used to study PD and DBS [9]–[19], but no prior work has developed the relationship between motor symptoms of PD in behaving rats and the effects of GPi-DBS. In order to address this, the work presented here provides a systematic characterization of behavior tuning in response to stimulation frequency and validation of the translational value of the 6-OHDA rodent model to study GPi-DBS.

Animals were evaluated using a suite of behavioral paradigms to probe their motor ability, mood and impulsiveness. We assayed their performance in three different states: naive (intact), hemi-Parkinsonian, and with stimulation (i.e., hemi-Parkinsonian state with unilateral GPi-DBS). Thus, each subject served as its own control and eliminated the need for multiple cohorts. In many DBS studies, animal and human, it has been found that high frequencies ($>$90 Hz) are more effective than low frequencies for stimulation in both GPi and STN [7], [17], [18], [20], [21]. In order to fully ascertain

Manuscript received September 26, 2013; revised March 29, 2014; accepted May 16, 2014. Date of publication June 12, 2014; date of current version November 13, 2014.

S. R. Summerson and B. Aazhang are with the Department of Electrical and Computer Engineering, Rice University, Houston, TX 77005 USA (e-mail: srsummerson@rice.edu; aaz@rice.edu).

C. T. Kemere is also with the Department of Electrical and Computer Engineering, Rice University, Houston, TX 77005 USA, and also with the Department of Neuroscience, Baylor College of Medicine, Houston, TX 77030 USA (e-mail: caleb.kemere@rice.edu).

Color versions of one or more of the figures in this paper are available online at http://ieeexplore.ieee.org.

Digital Object Identifier 10.1109/TNSRE.2014.2330515

behavior tuning with stimulation frequency, we considered a range of frequencies spanning untherapeutic and therapeutic regimes.

We found that high frequency (>100 Hz) GPi-DBS reduced akinesia and bradykinesia in a subpopulation of the rats, and improved motor asymmetry and ambulation across the entire population. Additionally, the subjects became more anhedonic with high frequency stimulation. This is the first report of findings for GPi-DBS and the conclusions are consistent with observations from human studies [3], [21]–[23]. Overall the results demonstrate the characteristic response of motor behavior to the stimulation frequency parameter and strongly support the validity of the hemi-Parkinsonian rodent model for studies of GPi-DBS.

II. Methods

A. Subjects and Study Design

Male Long-Evans rats (Charles River Laboratories) weighing 400–550 g were housed individually under a 12/12 h light/dark cycle. To facilitate behavioral training, animals were given a food restricted diet such that they reached approximately 85% of their initial weight. Water was given *ad libitum*, except preceding the sucrose preference task. All experiments were approved by the Institutional Animal Care and Use Committee of Rice University.

Two populations of rats were used. The first population ($n = 10$) was hemi-Parkinsonian and studied in a variety of motor tasks to understand how stimulation frequency tuned motor behavior. A rotation task determined the asymmetrical limb use attributed to the unilateral 6-OHDA lesion and the reduced asymmetry under 10 stimulation frequencies. This was further characterized in a cylinder task, where ipsilateral and contralateral forelimb wall touches were recorded for the same settings. The open field task was used to investigate the horizontal and vertical ambulation of the subjects in the hemi-Parkinsonian state and with five different stimulation frequencies. The second population of subjects ($n = 10$) was evaluated in motor and cognitive tasks in three possible states: naive (intact), hemi-Parkinsonian, and with GPi-DBS at a stimulation frequency verified to be therapeutic from the first population (130 Hz). This group was evaluated in a reaction time task to monitor the level of akinesia and bradykinesia in subjects, as well as to measure their level of impulsiveness. Additionally, anhedonia was measured via a sucrose preference task.

B. Electrode Implantation and 6-OHDA Lesions

Following behavior training and/or behavior evaluation in the naive state, the rats received a unilateral injection of 6-OHDA in the right hemisphere and were implanted with a stereotrode in the right entopeduncular nucleus (EP), the rat equivalent of the GPi. Prior to surgery, desmethylipramine (DMI, 10–20 mg/kg IP) was administered to protect noradrenergic neurons. Under anesthesia (0.5%–5% isoflurane in oxygen, buprenorphine 0.01-0.05 mg/kg SQ), 6-OHDA (2 μl of 4 μg/μl in 0.9% saline; Sigma, Zwijndrecht, The Netherlands) was stereotactically injected into the medial forebrain bundle (MFB, coordinates from Bregma: AP -4, ML 1.2, DV -8.1). In the same procedure, a platinum iridium or tungsten stereotrode ($R = 10k\Omega$; MicroProbes, Maryland, USA) was implanted in the EP (coordinates from Bregma: AP -2.5, ML 3, DV -7.9). Craniotomies were sealed with silicone elastomer (World Precision Instruments, Sarasota, FL, USA), and the electrode connector was affixed in place with 6–12 stainless steel skull screws, as exposed skull surface space allowed, and dental acrylic. The rats were given two days of post-operative care and all rats began the behavior tasks two weeks following the injection of 6-OHDA, which is sufficient time for a dopaminergic lesion to develop [24].

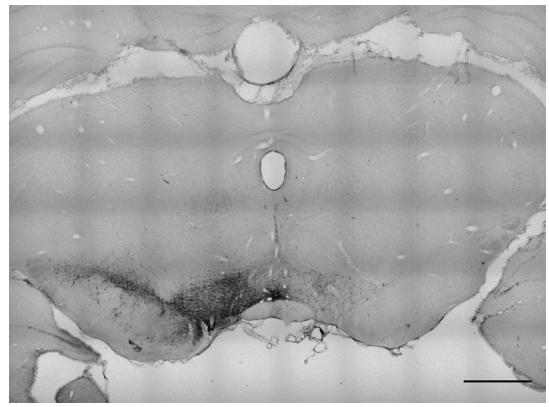


Fig. 2. Representative image of THir cells in the SNc on the left lateral and right lateral sides of a 50 μm slice. Scale bar is 1 mm. TH positive cells appear darker than the surrounding tissue.

C. Histology

Following the experiments, the rats were anesthetized and the stimulating sites were marked by electrolytic lesions. The rats were given an overdose of Euthasol ($0.5 - 1$ ml; Virbac AH Inc.) and then perfused intracardially with a 10% isotonic sucrose solution followed by 4% paraformaldehyde (PFA) in PBS. The brains were cryoprotected in a 30% sucrose solution in PFA (typically 4–5 days), then frozen in Tissue-Tek OCT and stored at $-80\,^{\circ}$C. Frozen brains were sliced along the coronal plane and 50 μm sections were immunostained for tyrosine hydroxylase (TH; primary rabbit anti-TH antibody, 1:200 dilution; and biotinylated goat anti-rabbit secondary antibody, 1:400 dilution). A red fluorescent Nissl stain was used (Neurotrace, Invitrogen, 1:200 dilution) and slices were mounted using ProLong Gold Antifade Reagent with DAPI. The slices were imaged using a Nikon A1-rsi Confocal Microscope and the number of TH immunoreactive (THir) cells was quantified using Nikon Elements software (Nikon, Tokyo, Japan).

Symptoms of PD are thought to become apparent after loss of a large fraction of dopaminergic cells. We quantified the extent of our unilateral 6-OHDA lesions both directly via histology and standard behavioral assays. Comparing the lesioned and unlesioned hemispheres, there was a significant 6-OHDA-induced depletion of $83.97 \pm 4.41\%$ (mean $\pm$ SEM) THir cells in the SNc (results of one-way ANOVA: $\mathrm{F}(1, 40) = 56.24$, $p < 0.001$; see Section II-F for explanation of ANOVA). A sample image in Fig. 2 demonstrates the considerable difference in THir cells in the left lateral and right lateral SNc. The positions of the electrode tips in the GPi, also depicted with gray shading in Fig. 3,

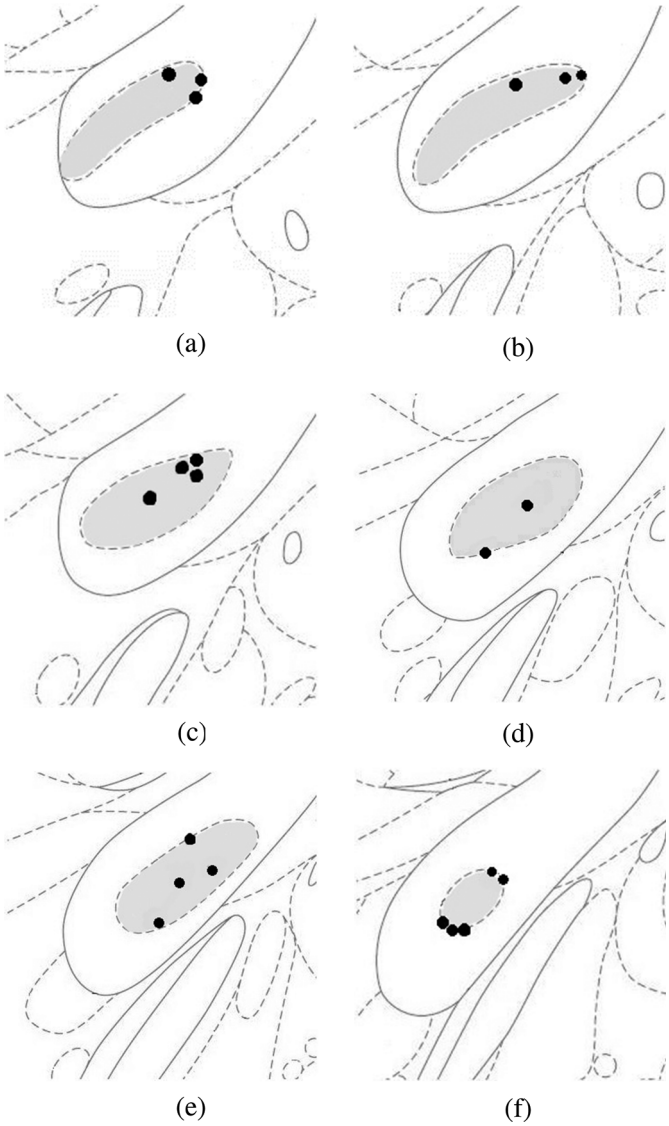


Fig. 3. Approximate locations of the electrode positions for all subjects with one marker per subject and the EP (GPi) shaded in gray. Each image is a depiction of a coronal section that is 2–4 mm lateral and 7–9 mm ventral from Bregma, with solid and dashed lines demarcating neighboring nuclei. (a) Section is -2.16 mm posterior to Bregma. (b) Section is -2.28 mm posterior to Bregma. (c) Section is -2.4 mm posterior to Bregma. (d) Section is -2.52 mm posterior to Bregma. (e) Section is -2.64 mm posterior to Bregma. (f) Section is -2.76 mm posterior to Bregma.

were localized by locating the electrolytic lesions using the confocal microscope. One black point per subject represents the position of each electrode.

D. Stimulation

The standard stimulation signal used in the PD rodent model consists of a sequence of brief bi-phasic constant-current square pulses delivered at a constant rate [15], [17]–[19]. The amplitude of the stimulation was tuned to the lowest current amplitude that produced noticeable improvement in the rats' spontaneous behavior in an open arena; the values ranged from 45–98 μA, with an average amplitude of 63.5$\pm$4.61 μA (mean $\pm$ SEM). For the rotation task and cylinder task, we characterized the performance of the rats between 40 and 175 Hz stimulation at intervals of 15 Hz. This set of frequencies was selected in order to fully establish a range of ineffective and effective stimulation frequencies. The results from these two tasks clearly demonstrate that there is a therapeutic threshold of stimulation, which appears to occur around 100 Hz, dividing lower, ineffective stimulation frequencies from higher, more effective stimulation frequencies. The open field task was performed for a subset of frequencies: 40, 85, 100, 115, and 160 Hz. This set of frequencies consist of a known untherapeutic frequency (40 Hz) and a known highly therapeutic frequency (160 Hz), as well as three frequency values around the so-called therapeutic threshold. For the reaction time task and sucrose preference task, we chose to perform the experiments using 130 Hz stimulation because this is found to be an effective stimulation frequency for GPi-DBS and previous work on STN-DBS of hemi-Parkinsonian rats found this value to be effective as well in improving the motor performance [17], [18]. In line with previous studies, we fixed the current to 65 μA for all subjects during 130 Hz stimulation for these two tasks.

The duration of the stimulation was up to 120 min/day, depending on the behavior task. After a period of stimulation, at least 12 h elapsed before a rat's performance was evaluated again under stimulation. This ensured that there were no carryover effects between periods of stimulation [17], [18], [25]. Anecdotally, the observable behavior of the rat changed instantaneously once stimulation was turned off and there appeared to be no long-term behavioral effects.

E. Behavioral Measures

Rotation Task: Methamphetamine induces rotation (circling behavior) in the direction ipsilateral to the SNc lesion and apomorphine induces rotation in the contralateral direction [18]–[20], [26]–[29]. The rotation task was performed on the rats $(n = 10)$ twice using each drug and the results were averaged. The number of rotations per minute is used as an indicator of extent of the lesion, i.e., the loss of dopamine function in 6-OHDA lesioned rats [19], [20], [27], [28], as this circling behavior is not present if striatal dopamine is not depleted. With effective DBS the number of rotations is attenuated. Methamphetamine dissolved in saline was administered IP (1.875 mg/kg) [17] under anesthesia (5% isoflurane in oxygen). Rats regained consciousness in 1-2 min and rested for an additional 15 min. This resting period allowed the methamphetamine to take effect in the rats. Rats were then placed in a cylindrical environment (diameter 30 cm, height 45 cm) made of clear acrylic and allowed to behave spontaneously. The task was performed similarly for apomorphine, except that apomorphine was dissolved in saline and administered SQ (0.1 mg/kg) [26], [27], [29].

The task consisted of 11 epochs. One epoch was allocated for assaying the rat in the hemi-Parkinsonian state (i.e., stimulation was off) and then 10 epochs were allocated for the 10 different stimulation frequencies ranging from 40 to 175 Hz. Each epoch was 2 min in duration and was followed by a control period that was 3 min in duration with stimulation off. The order of the epochs was randomized within each block. The block of eleven epochs was 2 h in duration and this design was dictated by the limited time of action of the drugs. The task was performed four

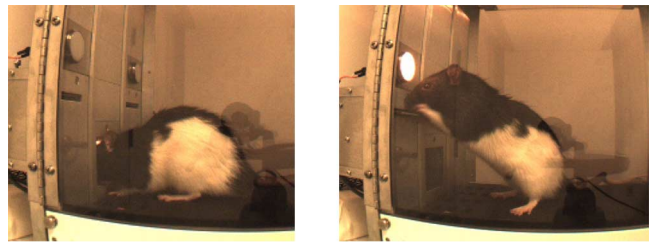
times per animal for each drug, in line with other rodent studies [18], [30]. Video data in 3-D was captured using a Microsoft Kinect (Microsoft, Redmond, WA, USA) and was processed in MATLAB to determine the angular movement of the rat over time.

Cylinder Task: A cylinder task is traditionally used to measure the asymmetric forelimb use in the hemi-Parkinsonian rat, with the extent of the asymmetry indicating the extent of the unilateral lesion induced by the 6-OHDA injection [15], [28]. In this task, the rat was placed in a cylindrical environment (inner diameter 20 cm, height 46 cm) and permitted to behave spontaneously. Rats $(n = 10)$ were observed while freely rearing 25 times and the proportion of paw presses with the limb ipsilateral to the 6-OHDA lesion was counted; the period of exploratory rearing is limited, which is why we required only 25 rears for test condition. This task was repeated while stimulation was administered for 10 different stimulation frequencies, with at least 30 s between periods of stimulation.

Open Field Task: The open field task is used to evaluate ambulation, which is measured via horizontal and vertical activity (i.e., rearing) [31]–[33]. The open-field task was conducted on a square arena, 1 m × 1 m, which was raised 1 m off the floor and marked into a grid dividing it into 25 equal-sized squares. Low lighting was used to illuminate the room and a camera was mounted on the ceiling above the arena. Video recordings were used to extract performance data. The number of squares traversed was recorded, which was calculated as the number of squares the rat occupied with at least three paws crossing the grid lines demarcating the square. Additionally, the number of rears, defined as the standing on its hind legs only, was counted. Each animal $(n = 10)$ was evaluated at most once per day for 25 min. The task was repeated five times per animal, with a different frequency each time, and the order of the frequencies randomized for each animal. Between animals, the arena was cleaned using Sani-wipes.

Reaction Time Task: Rats $(n = 10)$ performed a reaction time (RT) task (similar to [17]) which yielded measures of both motor and cognitive status. The task employs an operant conditioning box (Med Associates, inner dimensions: $30.5 \times 24.1 \times 21$ cm) equipped with two retractable levers flanking a liquid reward dispenser. A sensor at the dispenser detected when head insertions and withdrawals occurred. There were cue lights above each component, which indicated to the rat that an action be executed in relation to that component. The box was positioned inside an isolation chamber and time was recorded to a resolution of 10 ms.

The reaction time (RT) task was composed of four phases: a holding phase, lever-pressing phase, reward phase, and time-out phase. Each trial began with the cue light above the liquid reward dispenser turning on, indicating the rat should insert and hold its head in place for a random period (chosen uniformly between 0.6 and 1.5 s in steps of 0.1 s). This is depicted in Fig. 4(a). The hold period time reset any time the rat prematurely withdrew its head from the dispenser area, which is termed a premature response. Once the rat successfully completed this phase, the cue light above the liquid dispenser was extinguished, a random lever was extended (left and right lever extensions were equally likely) and the corresponding lever cue light was illuminated. The rat then withdrew its head and pressed the lever, as depicted in Fig. 4(b). Following depression of the lever, the rat was given a milk reward with 50% probability in order to increase the likelihood of an overall larger number of completed trials [35]. An inter-trial time out phase lasted 10 s, allowing rats time to drink and potentially exit the dispenser area prior to the next trial.



(a) (b)

Fig. 4. Depiction of the RT task. (a) Rat places its head above milk well for a random time interval, with an early head withdrawl termed a premature response. Time to correctly withdrawl head at end of interval is the reaction time. (b) Following correct head withdrawl a lever is extended and the time until lever depression is the motor time. (a) Holding. (b) Lever press.

We define three behavioral measures for this task: 1) RT, 2) motor time (MT), and 3) the proportion of premature responses (PPR). The RT was defined as the time between the lever extension and the withdrawal of the rat's head. This is a model of the rats' ability to initiate movement, which is impaired when in an akinetic state. Times longer than 1.5 s were disregarded as they are considered to be times not related to the task [16], [35]. The MT was measured as the time following the head withdrawal until the lever was pressed; times longer than 2 s were generally considered as not task-related (e.g., rat lost interest task) and thus were excluded from analysis [16], [35]. This measure relates to bradykinesia and how well the rats were able to execute a movement. Finally, the PPR was computed as the ratio of premature responses to total responses, i.e., premature responses plus correct responses

$$\text{PPR} = \frac{\text{Number of premature responses}}{\text{Number of premature } + \text{correct responses}}. \tag{1}$$

This metric indicates the impulsiveness of the rat [17].

The rats were trained on this task until their performance was stable, which took 4–6 weeks. The performance was considered stable if the means RT and MT were within the mean ± standard error of the mean (SEM) for the previous two days. Additionally, we required that the five-day sliding average PPR was within the five-day sliding mean ± SEM from the previous two days. Once stability was achieved, the rats were evaluated in the behavior box once a day for three consecutive days, which defined their performance in the naive state. Following surgery, the rats were retrained for three days to ensure that the behavior had not been unlearned during the post-op recovery period before they were assayed in the hemi-Parkinsonian state. The performance for the hemi-Parkinsonian state and the treated state with 130 Hz GPi-DBS was measured over nonoverlapping three consecutive day periods, one task per day.

Sucrose Preference Task: Given a choice, rats prefer sucrose-sweetened water to plain water, but this preference decreases in an anhedonic state [36]. Animals ($n = 10$) were deprived of water for 8 h to ensure that they were thirsty prior to the task. They were then allowed 1 h to drink freely from two identical bottles filled with water and a 1% sucrose solution. The sucrose preference index (SPI) was the metric associated with this task and is defined as

$$\text{SPI} = \frac{\text{grams of sucrose solution consumed}}{\text{grams of sucrose solution} + \text{water consumed}}. \quad (2)$$

This task was performed twice per state for each subject, with at least 24 h of water available *ad libitum* between tasks. The rats were assayed in the naive state, hemi-Parkinsonian state, and with 130 Hz GPi-DBS.

F. Statistical Analyses

Repeated measures ANOVA and MANOVA [37] tests were used to analyze the behavioral data and determine if the mean performance changed significantly across the various conditions. All computations were performed using MATLAB and IBM SPSS software. Sphericity is an underlying assumption of ANOVA analysis and degrees-of-freedom correction factors were used when this assumption was not met. Post hoc least significant differences (LSD) and Bonferroni tests were used for pairwise comparisons of the conditions [37]. We report the outcome here as $F(df_t, df_e)$, which is the F-distribution evaluated using the degrees-of-freedom of the treatment and error, df_t and df_e, respectively, with significance level p. For our experiment design, df_t is equal to $k - 1$, where k is the number of conditions tested (i.e., "treatments") and df_e is equal to $(k - 1)(n - 1)$ [37]. Additionally, correlations were calculated and their significance was evaluated using t-tests. For all statistical analysis, results were considered significant if the probability of incorrectly rejecting the null hypothesis of equal means (also known as Type I error), p, was less than 0.05.

III. Results

A. Effects of GPi-DBS on Motor Asymmetry

Rotation Task: To evaluate the efficacy of GPi-DBS on motor asymmetry, we used methamphetamine and apomorphine to induce locomotory rotation. We surveyed performance for 10 stimulation frequencies in addition to the hemi-Parkinsonian state without stimulation. Two-minute epochs of stimulation were preceded and followed by 3-min no-stimulation control periods. The rotation rates during the prior and post control periods were averaged and used to normalize the rotation rate of the stimulation epoch, i.e., the rotation rate with stimulation was divided by the average rotation rate from neighboring control periods so that the normalized rotation rate reflected the relative decrease in rotation when stimulation was administered. Results for the average normalized rotation rate for all conditions are shown in Fig. 5 for circling induced by (a) methamphetamine and by (b) apomorphine. The general trend for both drugs was that the normalized rotation rate decreased with increasing stimulation frequency. Additionally, we characterized the total angular distance traveled by the rat, which is the total angular movement in both directions (as opposed to the net movement in one direction which gives the rotation rate). The total angular movement for a stimulation epoch is normalized by the values for the preceding and following control epochs, as before, and then average across the population.

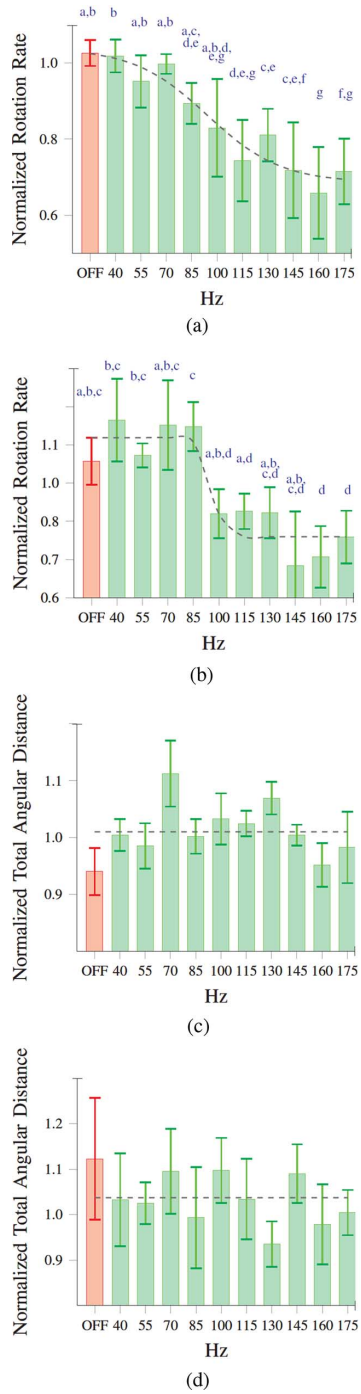


Fig. 5. Normalized rotation rate and total angular distance traveled are presented above for the rotation task using methamphetamine and apomorphine. Different alphabetical characters indicate significant differences determined from post-hoc LSD tests ($p < 0.05$). (a) Rotation rate with methamphetamine. (b) Rotation rate with apomorphine. (c) Angular distance with methamphetamine. (d) Angular distance with apomorphine.

Results for the average normalized angular distance is shown in Fig. 5 for circling induced by (c) methamphetamine and by (d) apomorphine.

For the methamphetamine rotation task, repeated measures ANOVA indicates that there is a significant difference in the normalized rotation rate across the stimulation conditions $(F(10, 90) = 4.625, p < 0.001)$. Post-hoc LSD tests indicate that a significant difference in the average normalized rotation rate from the off condition occurs for stimulation frequencies greater than 100 Hz, which is around where we hypothesize there is a therapeutic threshold. For frequencies of 115 Hz and larger, there is a significant reduction in the normalized rotation rate. In considering the total angular distance traveled (i.e., the rotational movement in both directions), we find that there is no significant change across the conditions $(F(10, 90) = 1.559)$; thus, net movement in one direction was reduced rather than a simple reduction in overall movement. We conclude that high-frequency GPi-DBS reduces the circling behavior induced by methamphetamine.

The same task was performed using apomorphine and again it was found that higher frequencies were more effective in reducing the normalized rotation rate of the subjects on average. There was a significant difference in average performance across the conditions $(F(10, 90) = 3.052, p < 0.01)$ and no significant change in total angular distance traveled was found $(F(10, 90) = 0.46)$, though post-hoc tests show that it not until 160 Hz that significant reduction in the rotation rate is achieved. We attribute this result to the short and intense time course of the drug. In general, the effects of the drug lasted between 25–50 min, which is less than half the time that the methamphetamine induced circling behavior. Additionally, rotation rates during peak epochs reached values greater than 50 rotations/min. Stimulation during these epochs was ineffective. Other studies have found that for high dosages of methamphetamine, STN-DBS was ineffective in reducing rotation rates in hemi-Parkinsonian rats, even for the stimulation frequencies up to 250 Hz [18], [30]. We believe that our results may be confounded by these extremely high periods of rotation caused by the apomorphine.

Cylinder Task: To further understand how GPi-DBS may improve the motor asymmetry in the hemi-Parkinsonian model as a function of the stimulation frequency, we performed a cylinder task on the rats $(n = 10)$ for the same 10 frequencies evaluated in the rotation task. We found that again motor asymmetry improves as stimulation frequency increases $(F(10, 90) = 4.455, p < 0.001)$. The results, shown in Fig. 6, are consistent with those found in the methamphetamine rotation task—frequencies about 100 Hz are effective in reducing the normalized rotation rate. For stimulation frequencies at 115 Hz and above, the average paw touch ratio is within errorbars of 0.5, which represents an equal number of touches by the contralateral and ipsilateral paws and indicates that the motor asymmetry is essentially eliminated with higher frequency GPi-DBS.

B. Effects of GPi-DBS on Movement

Open Field Task: The open field task was used to evaluate exploration and ambulation by measuring the number of squares traversed and the number of rears. The horizontal exploration of the rats was quantified in terms of the interior squares that they traversed (the inner 4×4 square area) and the outer squares that they traversed (the 16 outer squares that encompass the inner squares). The interior of the area is the most anxiogenic area, so normal animals spend more time in the corners and outer areas of the environment [33], [34]. Analyzing the animals across states, there were significant differences in the vectors of mean values of the dependent variables (repeated measures MANOVA; $F(12, 96) = 49.629, p < 0.001$).

There was no change in the average number of inner squares traversed for all of the conditions $(F(4, 32) = 0.88)$, which indicates that the anxiogenic state of the subjects was unchanged with stimulation. However, the dopaminergic lesion and subsequent GPi-DBS impacted the average number of outer squares traversed. There was a significant difference in the mean number of outer squares traversed by the rats across all states (repeated measures ANOVA; $F(4, 32) = 2.938, p < 0.05$), as shown in Fig. 7(a). Specifically, there was a significant increase in horizontal movement as the stimulation frequency increased, indicating that GPi-DBS improved horizontal ambulation in the subjects. The rearing rate, a measure of vertical ambulation, was also found to have a significant difference in the mean number of rears across conditions, as shown in Fig. 7(b) (repeated measures ANOVA; $F(4, 32) = 2.897, p < 0.05$). For stimulation at 115 and 160 Hz, there is a significant increased in the number of rears from the lowest stimulation frequency, 40 Hz.

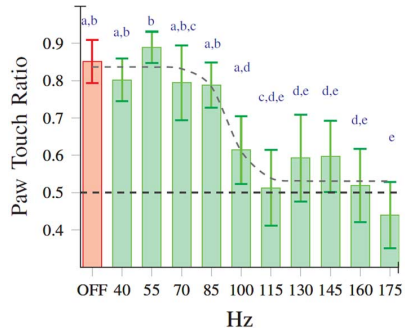


Fig. 6. Ipsilateral to total paw touch ratio in the cylinder task. Number of times the rat reared against the side of the cylinder environment and made contact using each forelimb was recorded. Total number of times the rat used the paw ipsilateral to the 6-OHDA lesion was divided by the total number paw touches to create the paw touch ratio. Different alphabetical characters indicate significant differences determined from post-hoc LSD tests $(p < 0.05)$.

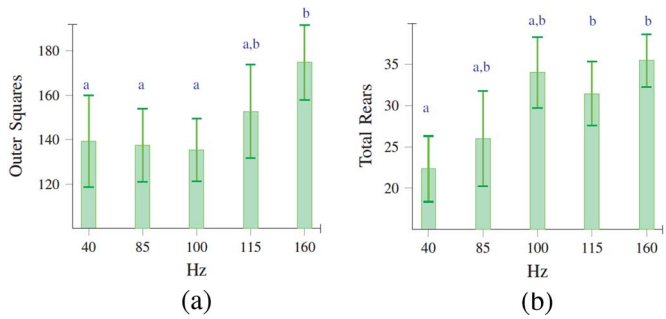


Fig. 7. Total number of outer squares traversed and number of rears during open field task. Different alphabetical characters indicate significant differences determined from post-hoc LSD tests $(p < 0.05)$. (a) Horizontal ambulation. (b) Vertical ambulation.

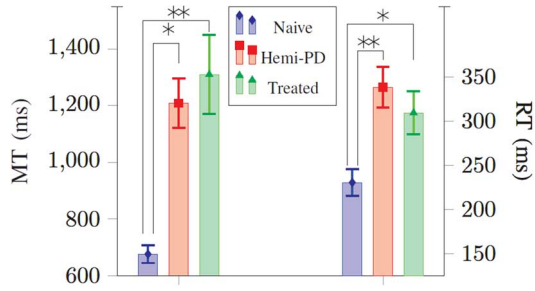


Fig. 8. Measures of akinesia and bradykinesia. Bars represent mean ± SEM. Mean MT and RT are shown on the left and right, respectively ($n = 10$). Significant differences were found between states. $^{**}p < 0.05$ and $^{**}p < 0.01$.

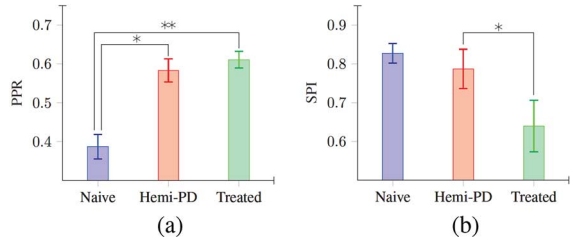


Fig. 9. Measures of cognition. Data is shown as mean ± SEM. (a) Mean PPR in the RT task ($n = 10$). Mean PPR across the states were determined to be significantly different. $^{*}p < 0.05$ and $^{**}p < 0.01$. (b) Mean SPI ($N = 10$). The mean SPI across the states was not equal. $^{*}p < 0.05$. (a) Impulsivity. (b) Sucrose preference.

Reaction Time Task: There are two motor metrics associated with the RT task: reaction time, i.e., the time to initiate a head withdrawal, and motor time, i.e., the time to press the extended lever. Compared to their naive behavior, hemi-Parkinsonian rats ($n = 10$) showed increased mean RTs and MTs with and without DBS (see Fig. 8). The effects of DBS treatment on motor metrics was complex. With DBS, no rat achieved the same level of performance as in the naive state, though some rats experienced a reduction in mean RT and MT. To evaluate the significance of the results, repeated measures MANOVA was first used to evaluate the multivariate trends. This test indicated that there was a significant difference in the vectors of mean values of the dependent variables, RT, MT and PPR ($F(6, 30) = 5.068, p < 0.001$). Hence, we proceeded with univariate tests of significance.

There was a significant difference in the mean MT performance of the rats across the clinical states ($F(1.177, 9.417) = 16.351$ with Greenhouse–Geisser correction, $p < 0.005$) and subsequent post-hoc analysis was done to evaluate pairwise differences. Under both LSD and Bonferroni tests, there was a significant increase in MT between the naive state and hemi-Parkinsonian state ($p < 0.005$), and no significant difference in mean MT between the hemi-Parkinsonian and treated states. For four out of 10 rats there was an improvement in mean MT and two out of 10 had no change in mean MT, but mean MT for the remaining four rats increased.

Similar trends were found in the analysis of RT data. Analyzing the group data, we found significant differences across states in the mean RTs (repeated measures ANOVA; $F(2, 16) = 11.885, p < 0.001$), that were significant pairwise (LSD and Bonferroni; naive and hemi-Parkinsonian state: $p < 0.02$, naive and treated state: $p < 0.05$). Three of the 10 rats had lower mean RTs when receiving stimulation than when hemi-Parkinsonian, while seven of out 10 rats had no change in mean RTs.

This lack of global improvement when DBS treatment was given is likely attributed to the fact that only a single current amplitude was used and there is high variation in terms what stimulation is effective across subjects [3], [18], [21], [24]. Since the parameters of the stimulation signal were fixed across the population of rats (65 μA current amplitude and 130 Hz stimulation frequency), it is not surprising that an overall therapeutic benefit of GPi-DBS was not found with respect to these two variables. The benefits of DBS are strongly tied to the stimulation amplitude and frequency, and generally must be tuned in order to maximize efficacy of the treatment [17], [18], [25], [30]. This is true not only in computational and experimental studies in animals, but in human studies as well [3], [4]. Although global motor improvement was not found, the quantified behavior is interesting in relation to the other variables examined throughout the experiment.

C. Effects of GPi-DBS on Cognition and Mood

Consistent with previous reports [17], we found hemi-Parkinsonian rats displayed increased impulsivity, as measured by premature responding (PPR), defined in (1). A significant difference in mean PPR was found (repeated measures ANOVA; $F(2, 16) = 20.387, p < 0.001$) and post-hoc analysis showed that the rats were significantly more impulsive in both the hemi-Parkinsonian and treated states relative to the naive state (LSD and Bonferroni; $p < 0.05$ and $p < 0.01$, respectively). The increased impulsivity between the treated and hemi-Parkinsonian state was not significant (LSD: $p = 0.114$). However, nine of 10 rats were most impulsive while receiving electrical stimulation.

In addition to impulsivity, we evaluated the rats for symptoms of depression. We found a significant change in the rats preference for sucrose [SPI Fig. 9(b)] defined in (2), across the three experimental states (repeated measures ANOVA; $F(2, 18) = 6.992, p < 0.01$). Pairwise comparisons showed that there was not a significant decrease in the mean SPI from the naive state to the hemi-Parkinsonian state. However, there was a significant decrease from the hemi-Parkinsonian state to the treated state (LSD and Bonferroni; $p < 0.05$). Thus, 130-Hz GPi-DBS increased anhedonia in the subjects.

IV. Correlation Analysis

We have demonstrated that when behavior is averaged over a moderately large cohort of animals, higher frequency GPi-DBS decreases hemi-Parkinsonian symptoms, such as pathological rotation and a lack of ambulation and rearing in an open field. However, it is unclear whether the variation in measured responses at higher frequencies or across different behavioral tasks simply reflects temporal randomness in DBS efficacy or actual graded differences in the responses of individual animals to GPi-DBS. Thus, we examined the correlation across subjects of responses at different frequencies within and across behavioral tasks. All p-values indicated here are from t-tests of significance.

We first examined the responses of different subjects in the open field to GPi-DBS. For frequencies of 85 Hz and higher, we found that an increased ambulation metric at one frequency was strongly correlated with increased ambulation metrics at other frequencies. For example, the amount of rearing observed with 85 Hz GPi-DBS is strongly positively correlated with the number of outer squares traversed during stimulation at frequencies of 85 Hz and above (all pairwise combinations: $r^2 > 0.5; p < 0.05$). Thus, at frequencies of 85 Hz and higher, benefits were consistent across behavioral measures.

We found similar results when examining methamphetamine-induced rotation. Normalized rotation rate under GPi-DBS for frequencies above 100 Hz were strongly correlated ($r^2 > 0.5; p < 0.01$). Thus, rats that have reduced rotation at one high frequency tended to also experience reduced rotation at other high frequencies. The same strong correlations were not as broadly observed for the rotation task with apomorphine, which is likely due to the highly variable rotation rate induced by the drug as previously discussed. However, the normalized rotation rates under apomorphine and methamphetamine were positively correlated for frequencies above 100 Hz ($r^2 > 0.4; p < 0.01$). Open field behavior presumably reflects slightly different, internally-generated mechanisms than pharmacologically-induced rotation. However, we found that the number of outer squares traversed in the open field was negatively correlated with the rotation rate of the rats under both apomorphine and methamphetamine for the highest frequency tested in the open field test, 160 Hz, suggesting therapeutic benefit in open field behavior was correlated with benefit under pharmacological rotation.

The open field and rotation tasks were studied in a different cohort of rats than the RT, sucrose preference, and open field tasks. We found similar correlated responses in these second subjects. With 130 Hz GPi-DBS, the motor times were positively correlated with reaction times ($p < 0.001$), so rats with lower levels of bradykinesia also tended to experience lower levels of akinesia. Regardless of DBS, increased impulsivity predicts anhedonia and a decrease in locomotion: PPR was negatively correlated with SPI ($p < 0.05$), number of squares ($p < 0.02$), and number of rears ($p < 0.05$).

V. Discussion

There are many reasons why the rodent model is a good model to study for PD and modulation of symptoms via DBS. Unlike human and nonhuman primate models of PD, there is rapid access to histopathological changes and it's easier to develop longitudinal studies due to the short lifespan of the animal. The hemi-Parkinsonian rodent model has been well developed [9]–[15], [17]–[19], [26], [29], [38], [39] and allows for simultaneous disease and control behavior in the same animal. Also, advances in transgenics have enabled new genetic rodent models [40]–[43]. Thus, it is ever important to characterize the effects of GPi-DBS in this model and verify the translational nature.

By comparing behaviors across frequencies and tasks in this work, we can draw two conclusions. First, that there is a therapeutic threshold for the stimulation frequency above which rodent GPi-DBS is effective in improving motor performance of the subjects. This agrees with existing literature on GPi-DBS in humans [2]–[7] and nonhuman primates [44], [45] which finds that higher frequencies are more effective. Second, that individual subjects display graded levels of response to DBS that is consistent across different behavioral measures. This graded response to DBS is consistent with what is observed in human studies, where stimulation parameters are tuned and adjusted over time to increase efficacy [46]–[48].

VI. Conclusion

Multiple variables were considered in this novel study of GPi-DBS in the hemi-Parkinsonian rat. We found that stimulation significantly improved motor asymmetry and vertical motor activity relative to the hemi-Parkinsonian behavior, particularly when stimulation at higher frequencies (> 100 Hz) was administered. Post-hoc statistical data analysis demonstrated that significant improvements in performance occurred for GPi-DBS beginning at around 100 Hz, which indicates that there is a therapeutic threshold of stimulation, below which stimulation tends to ineffective and above which it tends to effective. The strong correlations found for the frequencies within 15 Hz of this value additionally support this notion.

Responses of subjects were consistent across the tasks and we found that there was a graded responsive to GPi-DBS. The sucrose preference task showed a significant increase in anhedonic behavior between the hemi-Parkinsonian state and with 130 Hz stimulation, which matches results of human studies where depression is found to be a side effect of DBS treatment. We conclude that GPi-DBS is effective in treating the motor symptoms in the PD rodent model and the results agree with human studies. Previously, several studies of STN-DBS have been performed in the rodent model, but results on GPi-DBS were lacking. The data presented here serves as a foundation for future animal studies and models of GPi-DBS.

Acknowledgment

The authors would like to thank M. Bloom, A. Kunder, and T. Songkakul for their valuable assistance in animal training and data collection.

References

[1] J. L. Lanciego, N. Gonzalo, M. Castle, C. Sanchez-Escobar, M. S. Aymerich, and J. A. Obeso, "Thalamic innervation of striatal and subthalamic neurons projecting to the rat entopeduncular nucleus," *Eur. J. Neurosci.*, vol. 19, pp. 1267–1277, 2004.

[2] V. C. Anderson, K. J. Burchiel, P. Hogarth, J. Favre, and J. P. Hammerstad, "Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease," *Arch. Neurol.*, vol. 62, pp. 554–560, Apr. 2005.

[3] M. S. Okun, H. H. Fernandez, S. S. Wu, L. Kirsch-Darrow, D. Bowers, F. Bova, M. Suelter, C. E. Jacobson, X. Wang, C. W. Gorden, Jr., P. Zeilman, J. Romrell, P. Martin, H. Ward, R. L. Rodriguez, and K. D. Foote, "Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: The COMPARE trial," *Ann. Neurol.*, vol. 65, pp. 586–595, May 2009.

[4] J. Massano and C. Garrett, "Deep brain stimulation and cognitive decline in Parkinson's disease: A clinical review," *Front. Neurol.*, vol. 3, pp. 1–13, Apr. 2012.

[5] M. S. Okun and K. D. Foote, "Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: Will pallidal deep brain stimulation make a triumphant return?," *Arch. Neurol.*, vol. 62, pp. 533–536, Apr. 2005.

[6] L. Mallet, M. Schüpbach, K. N'Diaye, P. Remy, E. Bardinet, V. Czernecki, M. L. Welter, A. Pelissolo, M. Ruberg, Y. Agid, and J. Yelnik, "Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior," *Proc. Nat. Acad. Sci. USA*, vol. 104, pp. 10 661–10 666, May 2007.

[7] C. Hamani and Y. Temel, "Deep brain stimulation for psychiatric diseases: Contributions and validity of animal models," *Sci. Transl. Med.*, vol. 4, pp. 1–12, Jul. 2012.

[8] M. Troche, A. Brandimore, K. Foote, T. Morishita, D. Chen, K. Hegland, and M. Okun, "Swallowing outcomes following unilateral STN vs. GPi surgery: A retrospective analysis," *Dysphagia*, pp. 1–7, Mar. 2014.

[9] M. Alam, H. H. Capelle, K. Schwabe, and J. K. Krauss, "Effect of deep brain stimulation on levodopa-induced dyskinesias and striatal oscillatory local field potentials in a rat model of Parkinson's disease," *Brain Stimul.*, vol. 7, pp. 13–20, Jan.–Feb. 2014.

[10] W. Meissner, D. Harnack, N. Hoessle, E. Bezard, C. Winter, R. Morenstern, and A. Kupsch, "High frequency stimulation of the entopeduncular nucleus has no effect on striatal dopaminergic transmission," *Neurochem. Int.*, vol. 44, pp. 281–286, Mar. 2004.

[11] W. Meissner, G. Paul, T. Reum, R. Reese, R. Sohr, R. Morgenstern, and A. Kupsch, "The influence of pallidal deep brain stimulation on striatal dopaminergic metabolism in the rat," *Neurosci. Let.*, vol. 296, pp. 149–152, Dec. 2000.

[12] C. Perier, C. Marin, A. Jimenez, M. Bonastre, E. Tolosa, and E. C. Hirsch, "Effect of subthalamic nucleus or entopeduncular nucleus lesion on levodopa-induced neurochemical changes within the basal ganglia and on levodopa-induced motor alterations in the 6-hydroxydopamine-lesioned rats," *J. Neurochem.*, vol. 86, pp. 1328–1337, Sept. 2003.

[13] A. C. Sutton, W. Yu, M. E. Calos, L. E. Meuller, M. Berk, J. Shim, E. S. Molho, J. M. Brotchie, P. L. Carlen, and D. S. Shin, "Elevated potassium provides an ionic mechanism for deep brain stimulation in the hemiparkinsonian rat," *Eur. J. Neurosci.*, vol. 37, pp. 231–241, Jan. 2013.

[14] A. C. Sutton, W. Yu, M. E. Calos, A. B. Smith, A. Ramirez-Zamora, E. S. Molho, J. G. Pilitsis, J. M. Brotchie, and D. S. Shin, "Deep brain stimulation of the substantia nigra pars reticulata improves forelimb akinesia in the hemiparkinsonian rat," *J. Neurophysiol.*, vol. 109, pp. 363–374, Jan. 2013.

[15] J.-Y. Chang, L.-H. Shi, F. Luo, W.-M. Zhang, and D. J. Woodward, "Studies of the neural mechanisms of deep brain stimulation in rodent models of Parkinson's disease," *Neurosci. Biobehav. Rev.*, vol. 32, pp. 352–366, Oct. 2007.

[16] M. Amalric, H. Moukhles, A. Nieoullon, and A. Daszuta, "Complex deficits on reaction time performance following bilateral intrastriatal 6-OHDA infusion in the rat," *Eur. J. Neurosci.*, vol. 7, pp. 972–980, May 1995.

[17] Y. Temel, V. Visser-Vandewalle, B. Aendekerk, B. Rutten, S. Tan, B. Scholtissen, C. Schmitz, A. Blokland, and H. W. Steinbusch, "Acute and separate modulation of motor and cognitive performance in Parkinsonian rats by bilateral stimulation of the subthalamic nucleus," *Exp. Neurol.*, vol. 193, pp. 43–52, May 2005.

[18] G. C. McConnell, R. Q. So, J. D. Hilliard, P. Lopomo, and W. M. Grill, "Effective deep brain stimulation suppresses low-frequency network oscillations in the basal ganglia by regularizing neural firing patterns," *J. Neurosci.*, vol. 32, pp. 15 657–15 668, Nov. 2012.

[19] F. Rauch, K. Schwabe, and J. K. Krauss, "Effect of deep brain stimulation in the pedunculopontine nucleus on motor function in the rat 6-hydroxydopamine Parkinson model," *Behav. Brain Res.*, vol. 210, pp. 46–53, June 2010.

[20] P. Barnéoud, S. Parmentier, M. Mazadier, J. M. Miquet, A. Boireau, P. Dubédat, and J. C. Blanchard, "Effects of complete and partial lesions of the dopaminergic mesotelencephalic system on skilled forelimb use in the rat," *Neurosci.*, vol. 67, pp. 837–848, Aug. 1995.

[21] V. J. Odekerken, T. van Laar, M. J. Staal, A. Mosch, C. F. Hoffmann, P. C. Nijssen, G. N. Beute, J. P. van Vugt, M. W. Lenders, M. F. Contarino, M. S. Mink, L. J. Bour, P. van den Munckhof, B. A. Schmand, R. J. de Haan, P. R. Schuurman, and R. M. de Bie, "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): A randomised controlled trial," *Lancet Neurol.*, vol. 12, pp. 37–44, Jan. 2013.

[22] S. J. Moum, C. C. Price, N. Limotai, G. Oyama, H. Ward, C. Jacobson, K. D. Foote, and M. S. Okun, "Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome," *PLoS One*, vol. 7, pp. 1–8, Jan. 2012.

[23] S.-Y. Lim, S. S. O'Sullivan, K. Kotschet, D. A. Gallagher, C. Lacey, A. D. Lawrence, A. J. Lees, D. J. O'Sullivan, R. F. Peppard, J. P. Rodrigues, A. Schrag, P. Silberstein, S. Tisch, and A. H. Evans, "Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease," *J. Clin. Neurosci.*, vol. 16, pp. 1148–1152, Sep. 2009.

[24] K. Nowak, E. Mix, J. Gimsa, U. Strauss, K. K. Sriperumbudur, R. Benecke, and U. Gimsa, "Optimizing a rodent model of Parkinson's disease for exploring the effects and mechanisms of deep brain stimulation," *Parkinson's Dis.*, vol. 2011, pp. 1–19, Apr. 2011.

[25] A. M. Kuncel, S. E. Cooper, B. R. Wolgamuth, and W. M. Grill, "Amplitude- and frequency-dependent changes in neuronal regularity parallel changes in tremor with thalamic deep brain-stimulation," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 15, no. 2, pp. 190–197, Jun. 2007.

[26] M. T. Chen, M. Morales, D. J. Woodward, B. J. Hoffer, and P. H. Janak, "In vivo extracellular recording of striatal neurons in the awake rat following unilateral 6-hydroxydopamine lesions," *Exp. Neurol.*, vol. 171, pp. 72–83, Sep. 2001.

[27] R. J. Mandel, "Effect of acute L-Dopa pretreatment on apomorphine-induced rotational behavior in a rat model of Parkinson's disease," *Exp. Neurol.*, vol. 161, pp. 212–219, Jan. 2000.

[28] G. E. Meredith and U. J. Kang, "Behavioral models of Parkinson's disease in rodents: A new look at an old problem," *Mov. Disord.*, vol. 21, pp. 1595–1606, Oct. 2006.

[29] J. L. Hudson, C. G. van Horne, I. Strömberg, S. Brock, J. Clayton, J. Masserano, B. J. Hoffer, and G. A. Gerhardt, "Correlation of apomorphine- and amphetamine-induced turning with nigrostriatal dopamine content in unilateral 6-hydroxydopamine lesioned rats," *Brain Res.*, vol. 626, pp. 167–174, Oct. 1993.

[30] R. Q. So, G. C. McConnell, A. T. August, and W. M. Grill, "Characterizing effects of subthalamic nucleus deep brain stimulation on methamphetamine-induced circling behavior in hemi- Parkinsonian rats," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 20, no. 5, pp. 626–635, Sep. 2012.

[31] Y. H. Lin, A. H. Liu, Y. Xu, L. Tie, H. M. Yu, and X. J. Li, "Effect of chronic unpredictable mild stress on brain-pancreas relative protein in rat brain and pancreas," *Behav. Brain Res.*, vol. 165, pp. 63–71, Nov. 2005.

[32] A. J. Keeney and S. Hogg, "Behavioral consequences of repeated social defeat in the mouse: Preliminary evaluation of a potential animal model of depression," *Behav. Pharmacol.*, vol. 10, pp. 753–764, Dec. 1999.

[33] E. Choleris, A. W. Thomas, M. Kavaliers, and F. S. Prato, "A detailed ethological analysis of the mouse open field test: Effects of diazepam, chloriazepoxide and an extremely low frequency pulsed magnetic field," *Neurosci. Biobehav. Rev.*, vol. 25, pp. 235–260, May 2001.

[34] C. Del Seppia, L. Mezzasalma, E. Choleris, P. Luschi, and S. Ghione, "Effects of magnetic field exposure on open field behavior and nociceptive responses in mice," *Behav. Brain Res.*, vol. 144, pp. 1–9, Sept. 2003.

[35] A. Blokland, "Reaction time responding in rats," *Neurosci. Biobehav. Rev.*, vol. 22, pp. 847–864, Oct. 1998.

[36] L. Carnevali, F. Mastorci, G. Graiani, M. Razzoli, M. Trombini, M. A. Pico-Alfonso, R. Arban, A. J. Grippo, F. Quaini, and A. Sgoifo, "Social defeat and isolation induce clear signs of a depression-like state, but modest cardiac alterations in wild-type rats," *Physiol. Behav.*, vol. 106, pp. 142–150, May 2012.

[37] E. R. Girden, ANOVA: Repeated measures SAGE Univ. Paper Series Quantitat. Appl. Social Sci., 07084, 1992.

[38] M. Lundblad, M. Andersson, C. Winkler, D. Kirik, N. Wierup, and M. A. Cenci, "Pharmacological validation of behavioral measures of akinesia and dyskinesia in a rat model of Parkinson's disease," *Eur. J. Neurosci.*, vol. 15, pp. 120–132, Jan. 2002.

[39] L. H. Shi, D. J. Woodward, F. Luo, K. Anstrom, T. Schallert, and J. Y. Chang, "High-frequency stimulation of the subthalamic nucleus reverses limb-use asymmetry in rats with unilateral 6-hydroxydopamine lesions," *Brain Res.*, vol. 1013, pp. 98–106, July 2004.

[40] I. Magen and M. Chesselet, "Genetic mouse models of Parkinson's disease the state of the art," *Prog. Brain Res.*, vol. 184, pp. 53–87, 2010.

[41] D. Kirik, C. Rosenblad, C. Burger, C. Lundberg, T. Johansen, N. Muzyczka, R. Mandel, and A. Björkland, "Parkinson-like neurodegeneration induced by targeted overexpression of alpha-synuclein in the nigrostriatal system," *J. Neurosci.*, vol. 22, pp. 2780–2791, Apr. 2002.

[42] M. Decressas, B. Mattsson, and A. Björkland, "Comparison of the behavioural and histological characteristics of the 6-OHDA and alpha-synuclein rat models of Parkinson's disease," *Exp. Neurol.*, vol. 235, pp. 306–315, 2012.

[43] A. van Rompuy, E. Lobbestael, A. van der Perren, C. van den Haute, and V. Baekelandt, "Long-term overexpression of human wild-type and T240R mutant Parkin in rat substantia nigra induces progressive dopaminergic neurodegeneration," *J. Neuropathol. Exp. Neurol.*, vol. 73, pp. 159–174, Feb. 2014.
[44] K. W. McCairn and R. S. Turner, "Deep brain stimulation of the globus pallidus internus in the Parkinsonian primate: Local entrainment and suppression of low-frequency oscillations," *J. Neurophysiol.*, vol. 101, pp. 1941–1960, Apr. 2009.
[45] J. Zhang, Z. I. Wang, K. B. Baker, and J. L. Vitek, "Effect of globus pallidus stimulation on neuronal activity in the pedunculopontine tegmental nucleus in the primate model of Parkinson's disease," *Exp. Neurol.*, vol. 233, pp. 575–580, Jan. 2012.
[46] D. J. Pedrosa and L. Timmermann, "Review: Management of Parkinson's disease," *Neuropsychiatry Dis. Treat.*, vol. 9, pp. 321–340, Mar. 2013.
[47] F. Sprenger and W. Poewe, "Management of motor and nonmotor symptoms of Parkinson's disease," *CNS Drugs*, vol. 27, pp. 259–272, Apr. 2013.
[48] R. M. deSouza, E. Moro, A. E. Lang, and A. H. Schapira, "Timing of deep brain stimulation in Parkinson disease: A need for reappraisal?," *Ann. Neurol.*, vol. 73, pp. 565–575, May 2013.

Samantha R. Summerson (M'14) received the B.A. degree with honors in applied mathematics from the University of California, Berkeley, CA, USA, in 2006, the M.S. and Ph.D. degrees in electrical engineering from Rice University, Houston, TX, USA, in 2010 and 2014, respectively. She currently has a postdoctoral position at the University of California, Berkeley.

Her research interests include deep brain stimulation, movement disorders, information theory, and signal processing.

Behnaam Aazhang (F'99) received the B.S., M.S., and Ph.D. degrees in electrical engineering from University of Illinois, Urbana-Champaign, IL, USA, in 1981, 1983, and 1986, respectively.

In 1986 he joined the faculty of Rice University, Houston, TX, USA, where he is now the J. S. Abercrombie Professor in the Department of Electrical and Computer Engineering.

Caleb T. Kemere (M'12) received the Ph.D. degree in electrical engineering from Stanford University, Stanford, CA, USA.

He was a postdoctoral fellow at the Keck Center for Integrative Neurosciences at The University of California, San Francisco before joining the faculty of Rice University, Houston, TX, USA, in the Department of Electrical and Computer Engineering, in 2011.