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Frequency Matters: Beta Band Subthalamic Nucleus Deep Brain Stimulation Induces Parkinsonian-like Blink Abnormalities in Normal Rats

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Abstract

The synchronized beta band oscillations in the basal ganglia-cortical networks in Parkinson's disease (PD) may be responsible for PD motor symptoms or an epiphenomenon of dopamine loss. We investigated the causal role of beta band activity in PD motor symptoms by testing the effects of beta frequency subthalamic nucleus deep brain stimulation (STN DBS) on blink reflex excitability, amplitude, and plasticity in *normal* rats. Delivering 16 Hz STN DBS produced the same increase in blink reflex excitability and impairment in blink reflex plasticity in normal rats as occurs in rats with 6-OHDA lesions and PD patients. These deficits were not an artifact of STN DBS because when these normal rats received 130 Hz STN DBS, their blink characteristics were the same as without STN DBS. To demonstrate the blink reflex disturbances with 16 Hz STN DBS were frequency specific, we tested the same rats with 7 Hz STN DBS, a theta band frequency typical of dystonia. In contrast to beta stimulation, 7 Hz DBS exaggerated blink reflex plasticity as occurs in focal dystonia. Thus, without destroying dopamine neurons or blocking dopamine receptors, frequency specific STN DBS can be used to create PD- or dystonic-like symptoms in a normal rat.

Keywords

Blink Reflex; Parkinson's Disease; Basal Ganglia; Blepharospasm

Introduction

Several studies demonstrate the presence of exaggerated, synchronized beta band (10-30 Hz) activity throughout the basal ganglia-thalamo-cortical network in Parkinson's disease (PD) and animal models of PD (Brown *et al.*, 2001; Brown & Williams, 2005; Kuhn *et al.*, 2005; Sharott *et al.*, 2005). Beta band power in PD correlates with voluntary movement impairment (Kuhn *et al.*, 2009) and with improvement after dopaminergic treatment and

Deep Brain Stimulation (DBS) (Kuhn *et al.*, 2006; Ray *et al.*, 2008). The therapeutic effect of DBS appears to result from reducing beta band activity throughout the basal ganglia-cortical network (Meissner *et al.*, 2005). Only regular, high frequency DBS alleviates motor symptoms in PD (Dorval *et al.*, 2010). Low frequency DBS does not reduce beta band activity or attenuate PD symptoms (McConnell *et al.*, 2012). Indeed, low frequency DBS worsens motor deficits in PD patients (Timmermann *et al.*, 2004; Chen *et al.*, 2007) and 20 Hz transcranial stimulation subtly slows voluntary movements in healthy people (Pogosyan *et al.*, 2009). Nevertheless, another study fails to find any Parkinsonian-like effects on voluntary movement in rodents or non human primates receiving a 23 Hz oscillating current to the subthalamic nucleus (STN) (Syed *et al.*, 2012). These differences probably arise because the dynamic relationship between beta oscillations and voluntary movement makes it difficult to identify a direct causal role of these oscillations in PD. For example, beta band oscillation synchrony decreases in response to stimuli that cue voluntary movements and increases after a voluntary movement (Leventhal *et al.*, 2012).

One way to investigate the role of exaggerated beta oscillations on movement is through their effects on reflexes. This approach requires an animal model of PD that exhibits the same reflex abnormalities as PD patients. Following the development of PD-like exaggerated beta band oscillations (Sharott *et al.*, 2005), the 6-hydroxydopamine (6-OHDA) lesion rat model of PD manifests the same trigeminal blink abnormalities as PD patients, hyperexcitable blink reflexes, lack of habituation and impaired prepulse inhibition (Agostino *et al.*, 1987; Basso *et al.*, 1993; Schicatano *et al.*, 2000). Additionally, PD patients exhibit impaired blink reflex plasticity revealed by a protocol that utilizes high frequency stimulation of the supraorbital branch of the trigeminal nerve (Mao & Evinger, 2001; Battaglia *et al.*, 2006; Ryan *et al.*, 2014). Given that blink evoking stimuli can be delivered independently of ongoing voluntary movements, the trigeminal blink circuit provides an ideal motor system to investigate the motor effects of beta activity because reflex blinks are uncorrelated with the cues and motor planning that modulate beta oscillation amplitude with voluntary movements.

Our study tests the effects of STN DBS at beta (16 Hz), theta (7 Hz), and 130 Hz frequencies on blink reflex behavior and plasticity of normal rats. We compare these data with those from the 6-OHDA lesion model of PD. We posit that if exaggerated beta band activity is critical in the generation of Parkinsonian reflex and plasticity abnormalities, then only 16 Hz stimulation will induce a PD-like impairment in blink reflex behavior in normal rats.

Materials and Methods

Experiments were performed on fifteen male Sprague Dawley rats (350-550 g) maintained on a reversed 12 hour light/dark cycle and fed ad libitum. All experiments received approval by the Stony Brook University Institutional Animal Care and Use Committee and complied with all Federal, State, and University regulations and guidelines regarding the use of animals in research.

Surgery

Under general anesthesia (ketamine, 90 mg/kg and xylazine, 10 mg/kg), eight of the fifteen rats were implanted unilaterally with laboratory designed stimulating electrodes in the subthalamic nucleus (STN). Electrodes were implanted into the right STN stereotactically at AP: -3.8, ML: 2.5 based on the Paxinos and Watson stereotaxic atlas (Paxinos & Watson, 1998). Final STN electrode position was determined by recording through one of the DBS leads to find an increase in background activity as the electrode moved through the zona incerta into the STN. The stimulation electrodes were 4 twisted stainless steel Teflon coated wires (0.003 inch diameter bare, 0.0055 inch coated; A-M Systems, Everett, WA). After electrode implantation, rats were prepared for chronic recording of the left orbicularis oculi electromyogram (OOemg) and stimulation of the left supraorbital (SO) branch of the trigeminal nerve (Basso *et al.*, 1993; Evinger *et al.*, 1993). Wires were led subcutaneously to a connector embedded in a dental acrylic platform on the skull. The platform was attached to the skull by four stainless-steel screws. A silver wire connected to one of the stainless-steel screws served as the ground (Evinger & Manning, 1993; Dauvergne & Evinger, 2007).

Immediately before OOemg and SO electrode implantation, seven of the 15 rats received unilateral 6-hydroxydopamine (6-OHDA) lesions of the right Substantia Nigra Pars Compacta and medial forebrain bundle (Basso *et al.*, 1993). All rats received analgesic (ketorolac, 7 mg/kg) for at least 24 hrs after the surgery. Rats were alert and eating within 24 hrs of the surgery. The experiments began 10 days after surgery for the 6-OHDA injected rats and at least 1 week after the surgery for all other rats. After completion of experiments all rats were deeply anesthetized and perfused intracardially. The brains of rats with DBS electrodes were sectioned at 100 μ m and stained with cresyl violet to identify electrode location. The brains of rats with 6-OHDA lesions were sectioned at 40 μ m and immunohistochemically stained for Tyrosine hydroxylase to assess lesion magnitude (Basso *et al.*, 1993). Tyrosine hydroxylase staining revealed full unilateral lesions of the substantia nigra pars compacta in all seven 6-OHDA injected rats. Histological analysis revealed that STN electrode placement was correct in all but one of the rats. The rat with the incorrectly located electrode was not included in this study.

Procedures

In all experiments, the SO stimulus current was relative to the minimum current at which a 100 μ s stimulus reliably elicited the R1 component of a reflex blink, threshold (T). This current was determined at the beginning of each day for each rat and was held constant throughout that day's experiment. Threshold varied little across days (Ryan *et al.*, 2014). All data were collected at twice threshold (2T). Typical of all mammals except primates, this stimulus intensity evoked a strong R1 response and a smaller R2 component that occurred on slightly over half of the trials (Dauvergne & Evinger, 2007; Ryan *et al.*, 2014).

Rats underwent continuous biphasic 100 μ A 100 μ s STN DBS that began five minutes prior to threshold testing each day. Rats were observed closely for the duration of the day's experiments for signs of abnormal motor behavior. This stimulation intensity was chosen because it reliably affected trigeminal blink behavior without causing any irregular motor

behaviors in the rats or tissue damage in the STN. STN DBS was continued until the completion of that day's experiment.

Blink Excitability—We evaluated the effects of 16 and 130 Hz STN DBS on trigeminal blink excitability and amplitude in eight normal rats. Each day, rats underwent three blocks of twenty trials comprised of pairs of 2T SO with a 100 ms interstimulus interval. The intertrial interval was 20 ± 5 s. During each block, the rat received continuous 16 or 130 Hz STN DBS or No DBS; experiencing all three conditions each day. Each rat was tested in this paradigm for at least four days. As with clinical analysis of trigeminal blink reflex excitability in PD patients (Agostino *et al.*, 1987), we quantified blink excitability by dividing blink amplitude evoked by the second SO, the Test blink, by the amplitude of the blink elicited by the first SO, the Condition blink. Because our previous study (Basso *et al.*, 1993) demonstrated that the side contralateral to the 6-OHDA lesion exhibited the largest changes in blink excitability, we only examined OOemg activity contralateral to the STN stimulating electrode.

Blink Plasticity—To examine blink reflex plasticity we utilized a protocol previously designed to modify blink reflex gain (Mao & Evinger, 2001) that we recently adapted for use in rodents (Ryan *et al.*, 2014) in which we present high frequency stimulation (HFS) to the SO nerve. We delivered only a single frequency of STN DBS each day (Fig 1). Each day's data collection consisted of five blocks: (1) pre HFS; (2) HFS treatment; (3) immediately; (4) 30 min; and (5) 60 min post HFS. Pre and the three post HFS blocks were the same for all experiments. In these blocks, rats received 20 trials of a pair of 2T SO stimuli separated by 100 ms with an inter-trial interval of 20 ± 5 s. Each HFS treatment trial consisted of a single SO stimulus at 2T to evoke a reflex blink followed by five, 400Hz 2T SO stimuli delivered before the onset of the R2 component of the OOemg activity (HFS-B). The sixty HFS trials also occurred with a 20 ± 5 s interval. 6-OHDA lesioned rats underwent this learning protocol without DBS for at least eight consecutive days. Non-lesioned rats received No STN DBS, 7 Hz, 16 Hz, or 130 Hz STN DBS in a counterbalanced design for at least eight days per condition.

Data Collection and Analysis

Reflex blinks were monitored as rats moved freely in their home cage in a darkened room during their subjective night. OOemg signals were amplified, filtered at 0.3–5 kHz, collected at 4 kHz per channel and stored for later offline analysis on laboratory developed software (Dauvergne & Evinger, 2007). Blink amplitude was determined by integrating the rectified OOemg activity of each blink component.

In humans, HFS-B treatment depressed the R2 component of subsequent blinks (Mao & Evinger, 2001). We, however, investigated the effects of HFS-B on the R1 component of the blink reflex as it is the largest component of the blink reflex in non-primate mammals and exhibits the same changes in the HFS-B paradigm as R2 (Ryan *et al.*, 2014). We normalized all within day blink amplitude by dividing OOemg amplitude by the median pre HFS OOemg amplitude. As there was no difference in the post HFS blocks (Ryan *et al.*, 2014), post HFS blink amplitude was averaged over all three post treatment blocks. The normalized

mean pre HFS blink amplitude was subtracted from the normalized mean post blink amplitude. As the blink evoking stimulus remained constant throughout the day, we termed this measure of the change in blink amplitude following HFS *relative gain*.

Statistical tests of significance ($p < 0.05$) were performed with SPSS software (SPSS, Chicago, IL) using an Analysis of Variance Test (ANOVA) with post hoc Tukey tests, paired or independent t tests. Data are presented as the mean $\pm$ SEM.

Results

Patients with PD and 6-OHDA lesion models of PD exhibit increased excitability of the R2, but not the R1 component of trigeminal reflex blink (Agostino *et al.*, 1987; Basso *et al.*, 1993). If 16 Hz STN DBS creates a PD-like condition in reflex blinking in normal rats, then R2, but not R1 excitability should increase with 16 Hz STN DBS compared with the No DBS condition. As predicted, 16 Hz STN DBS significantly enhanced R2 excitability $153 \pm 42\%$ relative to the No DBS condition ($t_{(6)} = -4.0$, $p < 0.01$) but did not alter R1 excitability ($t_{(6)} = -0.81$, $p > 0.05$; Figs. 2A, 16 Hz; 2B). This increase in excitability is similar to that observed in the 6-OHDA lesioned rats when compared to normal rats (Powers *et al.*, 1997). In contrast, R1 and R2 excitability during 130 Hz STN DBS were not significantly different than during the No DBS condition (R1, $t_{(6)} = 1.35$ $p > 0.05$; R2, $t_{(6)} = -1.5$ $p > 0.05$, Figs. 2A, 130 Hz; 2B). Likewise, 7 Hz STN DBS significantly increased R2 excitability ($t_{(2)} = -3.0$, $p < 0.05$), but not R1 excitability ($t_{(2)} = 1.0$, $p > 0.05$, Figs. 2A, 130 Hz; 2B). Thus, 7 Hz STN DBS increased R2 excitability as occurs in the focal dystonia benign essential blepharospasm (Berardelli *et al.*, 1985) and 16 Hz STN DBS increased the R2 excitability of trigeminal blink reflexes of normal rats as occurs in PD patients (Kimura, 1973; Agostino *et al.*, 1987) and dopamine depleted rodents (Basso *et al.*, 1993).

Similar to the reduction in blink amplitude created by PD (Korosec *et al.*, 2006), 16 Hz STN DBS significantly reduced the amplitude of Condition reflex blinks in normal rats (Figs. 2A, 16 Hz vs. No DBS; 2C). 16 Hz STN DBS reduced R2 amplitude by $16.1 \pm 6.9\%$ ($t_{(9)} = 2.4$, $p < 0.05$) and R1 amplitude by $25.6 \pm 11.7\%$ ($t_{(7)} = 2.3$, $p < 0.05$) relative to the No DBS condition. As with excitability, 130 Hz STN DBS did not significantly affect trigeminal reflex blink amplitude (R1, $t_{(11)} = 1$, $p > 0.05$; R2, $t_{(10)} = 0.09$, $p > 0.05$; Figs. 2A 130 Hz vs. No DBS; 2C). 7 Hz STN DBS, a theta oscillation associated with dystonia (Silberstein *et al.*, 2003; Chen *et al.*, 2006), served as a test of whether the 16 Hz induced changes in reflex blink amplitude were frequency specific or a generalized effect of low frequency STN DBS. 7 Hz STN DBS caused an insignificant elevation of $10.8 \pm 9\%$ in R1 blink amplitude ($t_{(5)} = -1.3$, $p > 0.05$), but a significant increase of $77.2 \pm 39\%$ in R2 blink amplitude ($t_{(4)} = 2.2$, $p < 0.05$; Figs. 2A, 7 Hz vs. No DBS; 2C). The increased R2, but not R1, matches the change in blink amplitude caused by benign essential blepharospasm (Berardelli *et al.*, 1985).

High frequency SO stimulation modifies blink reflex gain in both humans (Mao & Evinger, 2001) and rodents (Ryan *et al.*, 2014). PD, however, impairs this reflex plasticity in patients off dopaminergic replacement therapy (Battaglia *et al.*, 2006). If 16 Hz STN DBS creates PD-like abnormalities in blink plasticity, then normal rats undergoing this stimulation frequency should fail to exhibit blink plasticity in this paradigm. In contrast, as the focal

dystonia benign essential blepharospasm enhances gain adaptation in this paradigm (Quartarone *et al.*, 2006), STN DBS at a theta frequency typical of dystonia (Silberstein *et al.*, 2003; Tsang *et al.*, 2012) should exaggerate blink plasticity.

A normal rat that received eight days of all four treatment conditions illustrated the effects of different frequencies of STN DBS on blink reflex plasticity (Fig. 3A). Similar to Ryan *et al.*, 2014, HFS-B treatment in the No DBS condition decreased the relative gain by $24.9 \pm 6.1\%$. HFS-B treatment during 130 Hz STN DBS caused a similar $30.1 \pm 5.9\%$ reduction in relative gain. In contrast, 16 Hz STN DBS reduced the blink depression from HFS-B treatment a mere $4.2 \pm 10.7\%$ whereas 7 Hz STN DBS theta band stimulation enabled HFS-B treatment to exaggerate the decrease in relative gain to $63.4 \pm 5.8\%$.

Averaging across all normal rats and days produced the same results in reflex plasticity as shown by the exemplar rat ($F_{(3, 258)} = 13.52$, $p < .001$; Fig. 3B). In the No DBS condition, HFS-B treatment significantly depressed subsequent R1 responses of normal rats by $23.3 \pm 3.0\%$ ($t_{(80)} = 7.02$, $p < 0.001$). During 130 Hz STN DBS, HFS-B treatment also significantly decreased blink amplitude by $19.7 \pm 3.0\%$ ($t_{(59)} = 6.92$, $p < 0.001$), which was not significantly different from normal rats that did not receive any STN DBS ($p > 0.05$). In normal rats, 16 Hz STN DBS reduced blink relative gain from HFS-B treatment to an insignificant $2.0 \pm 3.5\%$ ($p > 0.05$). This depression was not significantly different than the $6.6 \pm 4.4\%$ depression in blink gain observed in the separate group of rats with a 6-OHDA lesion ($p > 0.05$). Thus, HFS-B treatment created significantly more blink depression in the No DBS and 130 Hz STN DBS conditions than with 16 Hz STN DBS ($p < 0.001$ and $p < 0.05$, respectively). Rats that received 7 Hz STN DBS during HFS-B treatment exhibited an enhanced decrease in relative gain of $36.7 \pm 3.9\%$ ($t_{(56)} = 9.40$, $p < 0.001$) that was significantly more than gain reduction with No DBS ($p < 0.001$), 130 Hz STN DBS ($p < 0.001$) or 16 Hz STN DBS ($p < 0.001$). Thus, 16 Hz STN DBS in normal rats impaired blink reflex plasticity as occurs in PD patients (Battaglia *et al.*, 2006), whereas 7 Hz STN DBS exaggerated blink plasticity as occurs in the focal dystonia, blepharospasm (Quartarone *et al.*, 2006).

Discussion

These experiments employed STN DBS to demonstrate that specific frequencies of basal ganglia stimulation significantly altered reflex behavior in normal rats. We hypothesized that stimulation of the STN in normal rats at a beta band frequency typical of PD (Brown *et al.*, 2001; Brown & Williams, 2005; Kuhn *et al.*, 2005; Sharott *et al.*, 2005) would create the same blink reflex abnormalities present in PD patients and a rat model of PD, including, blink hyperexcitability, reduced blink amplitude, and impaired blink reflex plasticity. As predicted, 16 Hz STN DBS increased R2 blink excitability 153% relative to the No DBS condition (Fig. 2B). 16 Hz STN DBS also reduced trigeminal reflex blink amplitude by 25.6 and 16.1% for the R1 and R2 respectively (Fig. 2C). Thus, 16 Hz STN DBS created the same trigeminal blink reflex abnormalities as occur in the 6-OHDA lesion model of PD and PD patients.

We investigated blink reflex plasticity with a paradigm previously used to evaluate gain modification in normal subjects (Mao & Evinger, 2001) and patients with basal ganglia related disorders. In PD (Battaglia *et al.*, 2006), Huntington's disease (Crupi *et al.*, 2008), and Gilles de la Tourette syndrome (Suppa *et al.*, 2011), this paradigm revealed impaired gain modification, but in patients with the focal dystonia, benign essential blepharospasm, HFS treatment enhanced this plasticity (Quartarone *et al.*, 2006). We hypothesized that activating the basal ganglia at a beta band frequency characteristic of PD (Brown & Williams, 2005; Sharott *et al.*, 2005) would impair blink plasticity in a normal rat, whereas theta band activation typical of dystonia (Chen *et al.*, 2006; Tsang *et al.*, 2012) would enhance gain modification. We further predicted that stimulation at 130 Hz would not affect blink reflex plasticity in normal rats, as this frequency of STN DBS alleviates motor symptoms in PD and dystonic patients by reducing exaggerated low frequency basal ganglia oscillations (Dorval *et al.*, 2010; McConnell *et al.*, 2012). Activating the STN with a beta band frequency impaired blink plasticity in normal rats as occurred in PD patients (Battaglia *et al.*, 2006) and a rat model of PD (Fig. 3B). In contrast, driving the STN at a theta band frequency exaggerated gain adaptation in normal rats as occurred with the focal dystonia, benign essential blepharospasm (Quartarone *et al.*, 2006).

The changes in blinking were not a generalized effect of STN DBS because they were frequency specific. 130 Hz STN DBS, a commonly used frequency to treat movement disorders (Meissner *et al.*, 2005; Dorval *et al.*, 2010), did not affect blink excitability, amplitude, or plasticity (Figs. 2, 3). Stimulation at a theta band frequency typical of dystonia (Silberstein *et al.*, 2003; Chen *et al.*, 2006), however, increased R2 blink amplitude (Fig. 2C) and exaggerated blink plasticity (Fig. 3B) as occurs in the focal dystonia, benign essential blepharospasm (Quartarone *et al.*, 2006). R2 blink excitability increased with both 7 Hz and 16 Hz STN DBS as occurred with blepharospasm (Berardelli *et al.*, 1985), PD (Agostino *et al.*, 1987), and animal models of PD (Basso *et al.*, 1993). Thus, the effects of STN DBS were frequency specific. Depending upon the frequency of STN DBS, the same rat could exhibit normal behavior, PD blink abnormalities, or blepharospasm-like blink characteristics.

Although the circuit through which the basal ganglia modulate the excitability of the blink reflex is known (Basso & Evinger, 1996; Basso *et al.*, 1996), how the basal ganglia affects blink reflex plasticity is less understood. The cerebellum plays a significant role in gain changes for many brainstem reflexes, including the blink reflex (Pellegrini & Evinger, 1997; Blazquez *et al.*, 2004; Ryan *et al.*, 2014). It may be that synchronized beta and theta band oscillations in the basal ganglia disrupt normal cerebellar-basal ganglia interactions (Hoshi *et al.*, 2005; Jinnah & Hess, 2006). The stark difference in plasticity we observed between 7 Hz and 16 Hz STN DBS treatment support evidence that oscillatory activity at beta and theta band frequencies present in the basal ganglia with PD (Brown & Williams, 2005; Kuhn *et al.*, 2005) and dystonic patients (Silberstein *et al.*, 2003; Chen *et al.*, 2006; Tsang *et al.*, 2012), respectively, play a critical function in modulating this form of gain adaptation.

Synchronized beta band oscillatory activity has been postulated to play a role in PD motor symptoms, as this activity is present throughout the basal ganglia-cortical network in PD patients (Brown & Williams, 2005; Kuhn *et al.*, 2005) and animal models (Goldberg *et al.*,

2002; Sharott *et al.*, 2005). This aberrant activity correlates with symptom severity (Kuhn *et al.*, 2009; Pogosyan *et al.*, 2009) and movement effective treatments reduce the strength of beta band oscillations (Kuhn *et al.*, 2006; Ray *et al.*, 2008). The efficacy of DBS depends on the reduction of beta band activity as DBS frequencies that do not attenuate beta band activity also fail to ease Parkinsonian motor symptoms (McConnell *et al.*, 2012). Indeed, low frequency STN DBS worsens PD symptoms (Timmermann *et al.*, 2004; Chen *et al.*, 2007; Eusebio *et al.*, 2008). All of this evidence, however, is correlational.

Data from healthy humans support a causal relationship between beta band activity and voluntary motor performance. Using transcranial alternating current stimulation (TACS) in normal humans, investigators report that 20 Hz beta band stimulation significantly slowed the initial and peak velocity of voluntary movements, although there were no significant effects on reaction time or mean velocity (Pogosyan *et al.*, 2009). A later study reports that 20 Hz TACS reduced force development and peak force in a Go/No-Go task, while gamma stimulation (70 Hz) had the opposite effect (Joundi *et al.*, 2012). Although the effects were subtle, these experiments provide causal evidence for an antikinetic role of beta band activity in movement. Nevertheless, not all data support this ‘antikinetic’ role for beta oscillations in PD. The report that 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine injected monkeys become severely bradykinetic prior to the development of synchronized beta activity in the basal ganglia (Leblois *et al.*, 2007) is inconsistent with beta oscillations causing the bradykinesia of PD. Furthermore, delivering a 23 Hz oscillating current to the STN of normal rats and non human primates failed to create Parkinsonian-like motor abnormalities (Syed *et al.*, 2012). The focus of these studies, however, was on locomotion and arm movements, voluntary actions in which beta oscillations appear to play multiple roles (Leventhal *et al.*, 2012). Reflexes with PD, however, occur in an environment of exaggerated beta oscillations whose modulation is uncorrelated to the occurrence of reflex evoking stimuli. Driving the STN at a beta frequency in normal rats mimics the background upon which reflexes occur in PD or animal models of PD. Consistent with this situation, trigeminal reflex blink abnormalities with 16 Hz STN DBS are the same as with PD or rodent models of PD. This similar pattern of abnormalities in rodent models and patients probably results from the highly conserved organization of trigeminal blink circuits across mammals.

The current study utilized STN DBS to induce different frequency activity in the basal ganglia of normal rodents. Using this approach, we found that different frequencies created PD and dystonic blink plasticity abnormalities in the same rat. Thus, our approach offers the ability to reproduce Parkinsonian- and dystonic-like patterns of behavior without destroying dopaminergic neurons or blocking dopamine receptors. Our technique may offer a novel opportunity to investigate the neural bases of basal ganglia disorders.

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Figure 1.
HFS-B treatment protocol. Triangles show twice threshold 100 μ s supraorbital nerve stimulus. DBS, deep brain stimulation of the subthalamic nucleus.

Figure 2.

(A) Individual trials of the paired stimulus paradigm for a single rat without DBS (No DBS), 16 Hz STN DBS (16 Hz), 7 Hz STN DBS (7 Hz), and 130 Hz STN DBS (130 Hz). 7 and 16 Hz STN DBS increased the R2 Test response relative to Condition R2. 130 Hz STN DBS had no effect. Triangles show SO stimulus and arrows show R1 and R2 components. (B) Average percent change in reflex excitability for R1 and R2 components of the blink reflex for normal rats undergoing 16, 7 or 130 Hz STN DBS relative to the No DBS condition. 7 and 16 Hz STN DBS significantly increased the R2 excitability. 130 Hz STN DBS did not

alter R2 excitability. None of the stimulation frequencies affected R1 excitability. (C) Average percent change in R1 and R2 Condition reflex blink amplitude relative to the No DBS condition with 16, 7, and 130 Hz STN DBS. 16 Hz STN DBS significantly reduced the R1 and R2 components of the blink reflex while 7 Hz STN DBS significantly increased the R2 response of the blink reflex. Error bars are SEM. * $p < 0.05$

Figure 3.

(A) Average percent relative gain for a single rat with No DBS, 130, 16 and 7 Hz STN DBS. 16 Hz STN DBS reduced the relative gain while 7 Hz STN DBS increased the relative gain caused by HFS-B treatment. 130 Hz STN DBS had no effect on the relative gain. (B) Average percent relative gain for all normal rats receiving No DBS or 130, 16 or 7 Hz STN DBS. Rats that received 16 Hz STN DBS exhibited a significantly impaired relative gain similar to a group of 6-OHDA lesioned rats. Rats that received 7 Hz STN DBS exhibited an exaggerated gain change with HFS-B treatment. Error bars are SEM. *** $p < 0.001$