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Improved Efficacy of Temporally Non-Regular Deep Brain Stimulation in Parkinson's Disease

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Abstract

High frequency deep brain stimulation is an effective therapy for motor symptoms in Parkinson's disease. However, the relative clinical efficacy of regular versus non-regular temporal patterns of stimulation in Parkinson's disease remains unclear. To determine the temporal characteristics of non-regular temporal patterns of stimulation important for treatment of Parkinson's disease, we compared the efficacy of temporally regular stimulation with four non-regular patterns of stimulation in subjects with Parkinson's disease using an alternating finger tapping task. The patterns of stimulation were also evaluated in a biophysical model of the parkinsonian basal ganglia that exhibited prominent oscillatory activity in the beta frequency range. The temporal patterns of stimulation differentially improved motor task performance. Three of the non-regular patterns of stimulation improved performance of the finger tapping task more than temporally regular stimulation. In the computational model all patterns of deep brain stimulation suppressed beta band oscillatory activity, and the degree of suppression was strongly correlated with the clinical efficacy across stimulation patterns. The three non-regular patterns of stimulation that improved motor performance over regular stimulation also suppressed beta band oscillatory activity in the computational model more effectively than regular stimulation. These data demonstrate that the temporal pattern of stimulation is an important consideration for the clinical efficacy of deep brain stimulation in Parkinson's disease. Furthermore, non-regular patterns of stimulation may ameliorate motor symptoms and suppress pathological rhythmic activity in the basal ganglia more effectively than regular stimulation. Therefore, non-regular patterns of deep brain stimulation may have useful clinical and experimental applications.

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Keywords

Parkinson's disease; deep brain stimulation; bradykinesia; beta frequency oscillations

Introduction

High frequency deep brain stimulation (DBS) in the internal segment of the globus pallidus (GPi) or subthalamic nucleus (STN) is an effective and adjustable surgical treatment for motor symptoms of advanced Parkinson's disease (PD) (Benabid et al., 2009; Moro et al., 2010). Developed as a treatment for patients with advanced PD (Benabid et al., 1994; Siegfried and Lippitz, 1994; Limousin et al., 1995), DBS reduces tremor, rigidity, akinesia, and postural instability, and allows levodopa doses to be decreased (Limousin et al., 1998; Follett et al., 2010). Patients clinically diagnosed with idiopathic PD suffering from the cardinal motor symptoms are likely to receive benefit from DBS, with levodopa responsiveness predictive of its efficacy (Benabid et al., 2009).

The efficacy of DBS for PD is sensitive to the stimulation parameters, and high frequency (>100 Hz) DBS is more effective than low frequency (<100 Hz) stimulation (Rizzzone et al., 2001; Moro et al., 2002; Kuncel et al., 2006). The frequency-dependent efficacy of DBS is a key element for the proposed mechanisms of DBS, including stimulation-induced regularization of pathological neuronal activity (Birdno and Grill, 2008) and silencing of the stimulated neurons (Filali et al., 2004). The efficacy of DBS is also dependent on the amplitude, polarity, pulse width, and pattern of stimulation (Kuncel et al., 2004; Kuncel et al., 2006; Kuncel et al., 2007; Dorval et al., 2010; Birdno et al., 2012). However, the temporal pattern of stimulation stands out as a potentially important parameter space that has not been fully explored.

Non-regular temporal patterns of stimulation provide a means to probe the mechanisms of DBS (Birdno and Grill, 2008), and could potentially be used to expand the therapeutic efficacy of DBS (Feng et al., 2007; Rosin et al., 2011). Random patterns of stimulation are less effective at suppressing motor symptoms than regular stimulation in patients with essential tremor (ET) and PD (Birdno et al., 2008; Dorval et al., 2010; Birdno et al., 2012). In patients with ET, non-regular stimulation patterns are less effective at suppressing tremor than temporally regular stimulation because sufficiently long gaps in the stimulation train allow pathological activity to propagate through the stimulated nucleus (Birdno et al., 2012). However, the features of non-regular stimulation patterns that influence clinical efficacy in PD are unknown.

We applied different temporal patterns of stimulation to human subjects with PD to determine which features of non-regular stimulation cause it to be less effective than temporally regular stimulation. Surprisingly, we found that three non-regular patterns of stimulation significantly improved performance on a simple motor task compared to regular stimulation. Subsequently, using a computational model of DBS in the basal ganglia, we showed that the efficacy of various stimulation patterns was strongly correlated with their ability to suppress pathological oscillations in the beta frequency range. These results highlight the potential importance of the temporal pattern of stimulation as a means to enhance the efficacy of DBS.

Methods

The efficacy of five temporal patterns of high frequency DBS was quantified using an alternating finger tapping task in human participants with PD. As well, the effect of each

pattern on beta band oscillations was quantified in a computational model of the basal ganglia.

Human Subject Information

Individuals with DBS for PD undergoing implantable pulse generator (IPG) replacement surgery were recruited to participate in this study at Duke University Medical Center, Wake Forest Baptist Medical Center, and Emory University Hospital. Subjects were at least three months post DBS electrode implant/revision, capable of performing a simple finger tapping task, neurologically stable, and capable of understanding the study and consent form. The Institutional Review Boards at Duke University, Emory University, and Wake Forest University approved the study protocol, and subjects participated on a volunteer basis following written informed consent. Twenty-four subjects were consented for the study. Five subjects withdrew from the study before the experimental protocol began; nine subjects did not complete the experimental protocol; and ten subjects completed the protocol and were analyzed. DBS electrode target nucleus was either STN (7/10) or GPi (3/10). Subjects were asked to withhold PD medications for twelve hours prior to surgery, and most (7/10) complied. Demographic characteristics and stimulation settings for each subject are shown in Table 1.

Intraoperative Stimulation Protocol

Sedation and analgesia were withheld when possible (8/10) and local anesthetic (lidocaine) was used. Following removal and disconnection of the depleted IPG, a sterile connection was made between the extension cable and the signal generation equipment, allowing different temporal patterns of stimulation to be delivered through the implanted electrode.

Custom software (LabVIEW, National Instruments, Austin, TX, USA) on a battery-powered laptop computer generated the experimental patterns of stimulation. The analog voltage outputs (DAQCard™-6062E, National Instruments, Austin, TX, USA) were optically isolated (bp Optical Isolator with Probe, FHC Inc., Bowdoin, ME, USA) from the stimulation hardware. The subject's clinical stimulation parameters and contact settings were maintained when possible. Subjects with case (+) programming (4/10) were switched to a bipolar configuration and one of the clinically inactive electrode contacts was set as (+). Subjects (4/10) occasionally experienced uncomfortable side effects when the clinical DBS amplitude was applied—presumably because their clinical stimulation parameters were adjusted as the IPG battery voltage declined—and we used the maximum stimulation amplitude that did not cause discomfort. Some patients reported paresthesias from stimulation, but there were no other adverse events.

Stimulation Patterns

We compared bradykinesia during DBS-off (*Baseline*) to temporally regular DBS at 185 Hz (*Regular*) and to four non-regular temporal patterns of DBS (Fig. 1A) named according to their dominant feature or the shape of their instantaneous pulse frequency (IPF) distribution (Birdno et al., 2012). All patterns had a geometric mean frequency of 185 Hz (Supplementary Table 1). The *Absence* and *Presence* patterns were both periodic with low entropy (<1 bits/pulse) and characterized by either short periods absent of pulses or the presence of short bursts of pulses, respectively. The pauses and bursts both occurred at 4.4 Hz. The *Uniform* and *Unipeak* patterns were highly irregular (high entropy: ~5.5-5.6 bits/pulse) and were created from log-uniform distributions of IPFs. Although the *Unipeak* pattern was created from a wider log-uniform distribution of IPFs (44-720 Hz) than the *Uniform* pattern (90-360 Hz), the two patterns had the same entropy (Dorval, 2008).

Motor Performance Measurements

Motor performance was quantified using an alternating finger tapping task (Burns and DeJong, 1960; Giovannoni et al., 1999; Homann et al., 2000; Pal et al., 2001; Taylor Tavares et al., 2005). The subject's hand contralateral to stimulation was placed on a two-button computer mouse and the subject was asked to press alternately each button during 20 s trials (Fig. 1B and C). Trials were repeated every two minutes as we cycled through all the patterns with four-minute stimulation on and four-minute stimulation off epochs. The log-transformed coefficient of variation of tap duration is a statistical measure of variability of tap duration that is significantly correlated with the Unified Parkinson's disease rating scale (UPDRS) motor score, particularly with the bradykinesia subscore (Taylor Tavares et al., 2005), and was the primary measure of motor task performance across stimulation conditions. Because of the time course of the effects of DBS on motor symptoms in PD (Temperli et al., 2003; Waldau et al., 2011), the second data collection epoch near the end of each stimulation condition was analyzed unless it was missing, in which case the first data collection epoch served as its replacement. Furthermore, only button presses made with the index finger were analyzed because experimenter observations, *post hoc* data analysis, and further analysis of previously published data used to validate the alternating finger tapping task (Taylor Tavares et al., 2005) revealed that this was a more robust outcome measure (see Supplementary material). The same trends in the data were observed when averaging index finger motor performance during the early and late data collection epochs and when averaging the motor performance during the early and late data collection epochs for both fingers separately. In this repeated measures experimental design, we quantified bradykinesia in subjects at *Baseline* (DBS off) and during all five stimulation patterns. After the *Baseline* condition, the order of stimulation pattern presentation was randomized for each patient, and subjects were blinded to the stimulation conditions. Finger tapping task performance is weakly affected by age and gender (Pal et al., 2001), but the repeated measures experimental design mitigated the risks of variance and bias introduced by subject demographic characteristics. After completing the experimental protocol, the sterile connection between the extension cable and the stimulus-generating equipment was disengaged, and the IPG replacement surgery was completed.

Data Analysis and Statistics

Data collected through LabVIEW were processed using custom scripts in MATLAB R2009b (Mathworks, Natick, MA, USA) to extract click durations from the alternating finger tapping task. Technical outliers were removed by discarding extremely short clicks that were artifacts of the computer mouse clicking apparatus (debouncing; visual inspection of click duration histograms). JMP 9 (SAS Institute, Inc., Cary, NC, USA) and StatView 5.0.1 for Windows (SAS Institute, Inc., Cary, NC, USA) were used to conduct the statistical analyses. Experimental data were analyzed using repeated measures analysis of variance (ANOVA) with log-transformed coefficient of variation of the index finger tap duration as the repeated measure in each subject. The log-transformed coefficient of variation of the index finger tap intervals and the log-transformed number of index finger taps per 20 s data collection epoch are alternative motor performance measures that were also analyzed using the repeated measures ANOVA model. Fisher's protected least significant difference (PLSD) test was used to make *post hoc* comparisons across experimental conditions. Pearson's correlation coefficient was used to assess correlation strength. Paired t-tests were performed to assess the effects of bursts, pauses, and irregularity, *per se*, in data that were pooled across stimulus condition. Statistical significance was defined at $\alpha = 0.05$.

Computational Model of the Basal Ganglia

A biophysical model of the basal ganglia in a PD state was used to determine the effect of the different patterns of stimulation on oscillatory activity in model neurons (Rubin and

Terman, 2004; So et al., 2012). The computational model included the STN, GPi, and external globus pallidus (GPe), and each nucleus contained 10 single compartment neurons. Each GPe neuron sent inhibitory projections to two STN neurons, two GPi neurons, and two other GPe neurons. STN neurons sent excitatory projections to two GPe neurons and two GPi neurons (Fig. 1D). The biophysical properties of each neuron type were validated against experimental data (Terman et al., 2002; Rubin and Terman, 2004; So et al., 2012), and are described in detail elsewhere (So et al., 2012). Constant currents were applied to neurons in each nucleus to represent inputs from afferent projections that were not included in the model and produced firing rates that were consistent with observations in non-human primate models of PD and human patients with PD (Bergman et al., 1994; Starr et al., 2005; Steigerwald et al., 2008; Wichmann and Soares, 2008). STN and GPi neurons received applied current of $33 \mu\text{A}/\text{cm}^2$ and $21 \mu\text{A}/\text{cm}^2$, respectively. Variability was added to the model by delivering a constant current to each GPe neuron randomly drawn from a normal distribution centered around $8 \mu\text{A}/\text{cm}^2$ with a standard deviation of $2 \mu\text{A}/\text{cm}^2$. STN DBS was applied by delivering the desired pattern of current pulses (amplitude $300 \mu\text{A}/\text{cm}^2$; pulse width 0.3 ms) to each STN neuron. Simulations were implemented in MATLAB R2009b with equations solved using the forward Euler method with a time step of 0.01 ms and a total simulated time of 20 s.

Neurons in all nuclei exhibited strong oscillatory activity in the beta frequency range centered around 20 Hz. This oscillatory activity was spontaneously generated in the GPe-STN subcircuit, which possesses pattern generator qualities and is a possible source of oscillations in the basal ganglia (Bevan et al., 2002). Exaggerated beta band oscillatory activity is implicated in the pathophysiology of PD (Brown, 2003; Priori et al., 2004; Galvan and Wichmann, 2008; Bronte-Stewart et al., 2009) and changes in beta band oscillatory power are correlated with changes in symptoms during DBS (Silberstein et al., 2005; Kühn et al., 2008). Therefore, we quantified the effect of different stimulation patterns on the oscillatory activity in the primary output nucleus of the basal ganglia, the GPi. Spectrograms of the GPi spike times were generated using the Chronux neural signal analysis package (www.chronux.org) and MATLAB R2009b. We constructed the average multitaper spectrograms from GPi spike time data across all 10 GPi neurons using a 2 s sliding window and a 0.1 s step size. Since the frequency of the oscillatory activity could change over time as the stimulation was delivered, we quantified beta band power by evaluating the time-integral of the peak power density in the beta frequency range (13-35 Hz). These values were log-transformed and termed *Beta Band Power*.

Results

We measured bradykinesia in subjects with PD in a single intraoperative session while applying different temporal patterns of DBS to determine which characteristics of non-regular stimulation influenced its efficacy. Motor performance was quantified using the log-transformed coefficient of variation of index finger tap duration (Log CV Duration) during alternating finger tapping, and DBS improved performance in this task (Fig. 2). Repeated measures ANOVA revealed that the variability of finger tap duration was dependent on the pattern of DBS ($F = 7.989$, $p < 0.001$). In accordance with previous studies showing that DBS ameliorates motor symptoms in PD (Taylor Tavares et al., 2005; Dorval et al., 2010), post-hoc testing revealed that tap duration variability was greater during *Baseline* (DBS off) compared to *Regular* DBS ($p = 0.016$). Furthermore, tap duration variability was greater during *Baseline* compared to all the applied patterns of DBS individually ($p < 0.05$), indicating that all patterns of stimulation improved motor performance compared to the DBS off condition.

Post-hoc testing also revealed significant differences between stimulation patterns. During *Absence*, *Presence*, and *Uniform* DBS, the tap duration variability was lower than during *Regular* DBS ($p=0.007$, $p=0.031$, and $p=0.028$, respectively), indicating that these patterns improved bradykinesia in PD more effectively than the temporally regular stimulation pattern used clinically. Motor task performance (Log CV Duration) during the *Unipeak* and *Regular* patterns was similar. Consequently, tap duration variability during the *Absence*, *Presence*, and *Uniform* stimulation patterns was lower than during the *Unipeak* pattern ($p=0.018$, $p=0.069$, and $p=0.063$, respectively). When individually added to the repeated measures ANOVA statistical model, there was not a significant effect of surgical target (GPi and STN: $p = 0.21$), medication state ($p = 0.42$), sedation status ($p=0.54$), or switching to a bipolar electrode configuration ($p = 0.75$).

The responses to the different temporal patterns of stimulation were consistent across subjects. In 9/10 subjects, motor performance was better during the *Absence* and *Uniform* patterns compared to the *Regular* pattern. Motor performance was superior during *Presence* DBS compared to *Regular* stimulation in 7/10 subjects. Motor performance was improved during stimulation compared to *Baseline* in 80-100% of the subjects depending on the pattern.

Motor performance during the stimulation patterns was weakly correlated ($p = 0.071$, $R^2 = 0.076$) with motor performance during the preceding stimulation off period (Fig. 3A). This suggested that changes in finger tap duration variability between stimulation patterns were caused by the stimulation patterns themselves, and were not a reflection of fluctuations in baseline motor performance. Instead, and consistent with the time course of the action of DBS in PD (Temperli et al., 2003; Waldau et al., 2011), motor performance during the stimulation off period following each stimulation pattern reflected the motor performance during the preceding pattern of stimulation, as demonstrated by significant correlations between finger tap duration variability during the stimulation pattern and during the subsequent stimulation off periods ($p = 0.0019$, $R^2 = 0.20$; Fig. 3B).

The log-transformed coefficient of variation of the intervals between finger taps (log CV Interval) exhibited the same pattern of motor performance across stimulation patterns as log CV Duration (Fig. 4A). The finger tap timing was the most irregular, on average, during *Baseline* and the *Unipeak* pattern of stimulation, and the average log CV Interval during *Absence*, *Presence*, and *Uniform* DBS was lower than it was during *Regular* DBS. However, average differences in log CV Interval across patterns of stimulation were small, and the repeated measures ANOVA did not reveal a statistically significant effect of DBS pattern ($p = 0.44$). The log-transformed rate of finger tapping exhibited a similar dependence on stimulation pattern. The fewest button presses occurred during *Baseline* (stimulation off), and the most occurred during the *Presence* pattern of stimulation (Fig. 4B). However, the mean differences in tapping rates between the patterns of stimulation were small relative to the variance, and the repeated measures ANOVA did not reveal a significant effect of DBS pattern ($p = 0.45$).

We discovered that some temporal patterns of DBS improved motor performance more than regular stimulation, but the original goal was to determine which features of the stimulation patterns influenced the efficacy of DBS. Therefore, we evaluated the effects of bursts, pauses, and irregularity in the stimulation patterns by pooling motor performance data across stimulation trains that shared the feature of interest (Biprdno et al., 2012). We pooled data during *Presence* and *Unipeak* DBS into a “Bursts” group and the remaining patterns into a “No Bursts” group; measurements made during *Absence* and *Unipeak* DBS were pooled into the “Pauses” group; and measurements from *Uniform* and *Unipeak* DBS were pooled

into the “Irregular” group. Paired t-tests did not reveal a significant effect of bursts, pauses, or irregularity on the log CV Duration, log CV Interval, or tapping rate (Fig. 5).

It is possible that the effects of different temporal patterns of stimulation were explained by statistical properties of the patterns rather than being a direct result of the patterns themselves. However, there were no significant correlations between mean log CV Duration and several statistical descriptors of the stimulation patterns (Supplementary Table 1) including the pattern maximum IPF ($p = 0.53$), mean IPF ($p = 0.62$), mean pulse rate ($p = 0.82$), or entropy ($p = 0.87$).

A biophysical model of STN-DBS was used to quantify the effects of different temporal patterns of stimulation on beta band oscillations in the model GPi. The averaged multitaper spectrograms from the GPi spike time data revealed prominent oscillatory activity that was suppressed by DBS (Fig. 6A). All DBS patterns suppressed *Beta Band Power* compared to *Baseline*, and the relative effects of different patterns on *Beta Band Power* mirrored their effects on the experimental measures of motor function (Fig. 6B). Indeed, there was a strong correlation ($p = 0.007$, $R^2 = 0.87$) between *Beta Band Power* and log CV Duration (Fig. 6C). Furthermore, *Absence*, *Presence*, and *Uniform* DBS suppressed *Beta Band Power* more than *Regular* and *Uniform* DBS.

Discussion

Quantitative measurement of the effects of different temporal patterns of DBS on bradykinesia in subjects with PD and oscillatory activity of model neurons revealed three central findings. First, the pattern of stimulation, and not simply the stimulation rate, was an important factor in the clinical efficacy of DBS, as demonstrated by the different levels of performance on a simple motor task during different temporal patterns of stimulation all of which had the same mean frequency. Second, some non-regular patterns of stimulation relieved motor symptoms in PD more effectively than the temporally regular stimulation pattern used clinically. Third, the differential efficacy of DBS patterns was strongly correlated with the pattern's ability to suppress beta band oscillatory activity in a computational model of the basal ganglia (Fig. 6C).

The log-transformed coefficient of variation of tap duration is significantly correlated with the bradykinesia subscore of the UPDRS (Taylor Tavares et al., 2005), suggesting that the quantitative intraoperative measurements may be predictive of functional change. Secondary motor performance outcome measures (log CV Interval and log-transformed number of clicks) supported the primary motor performance outcome measure (log CV Duration). The correlation between log CV Interval and UPDRS motor scores is weaker than the correlation between log CV Duration and UPDRS motor scores (Taylor Tavares et al., 2005). The rate of finger tapping can also be used to quantify motor performance during an alternating finger tapping task (Dorval et al., 2010; Burns and DeJong, 1960; Giocannoni et al., 1999; Pal et al., 2001), and it has also been correlated with UPDRS motor scores (Homann et al., 2000). Although statistically significant differences in secondary motor performance measures were not observed, the data mirrored the log CV Duration data. There were, however, two discrepancies of note. First, performance quantified by the log CV Interval during *Unipeak* DBS was poor. In fact, according to this measure, it was slightly worse than motor task performance during *Baseline*. Second, the tapping rate data indicate that fewer clicks occurred during *Absence* DBS than during *Regular* DBS. Therefore, this contradicts that motor task performance--quantified by the tap duration variability--during *Absence* DBS was significantly better than during *Regular* DBS.

Conducting experiments during the IPG replacement surgery uniquely enabled the present experiments by allowing direct connection to the brain lead. Patients had a stable electrode-tissue interface, clinically relevant contact selections, and stimulation parameters with demonstrated clinical efficacy. Performing these experiments during the DBS lead implantation surgery, between the lead implant and the IPG implant, or in the immediate postoperative period is undesirable because of unproven clinical efficacy and transient effects of electrode implantation. However, the intraoperative setting limited trial durations, so the effects of the patterns of stimulation may not be fully developed and differences across patterns may be underestimated.

We used a finger tapping task with quantitative measures that are correlated with UPDRS motor scores (Homann et al., 2000; Taylor Tavares et al., 2005). The correlations between log CV Durations and the bradykinesia and rigidity UPDRS motor subscores are significant (Taylor Tavares et al., 2005), but it remains unclear whether these non-regular patterns of stimulation would ameliorate other parkinsonian motor signs. Although recording UPDRS motor scores during the intraoperative experiment would provide useful supplementary information, the feasibility of such ratings was limited by the intraoperative experimental paradigm. Instead, UPDRS motor score improvements across stimulation patterns were predicted from log CV Duration values using the correlation between these two variables (Supplementary Fig. 1C). Changes in log CV Duration from *Baseline* for each patient were multiplied by the correlation coefficient ($R = 0.58$) and scaled by the gain (80 UPDRS motor points per 0.75 log unit) to predict stimulation-induced shifts in UPDRS motor scores across stimulation patterns. The difference in log CV Duration scores between *Regular* stimulation and *Absence*, *Presence*, and *Uniform* patterns represented an improvement of 12-15 UPDRS motor score points on average, suggesting that these temporal patterns of stimulation provide clinically meaningful improvement over temporally regular stimulation.

Oscillatory and synchronized neural activity in specific frequency bands appear to be related to motor performance in patients with PD (Brown, 2003; Priori et al., 2004; Galvan and Wichmann, 2008; Bronte-Stewart et al., 2009), and the non-regular patterns of stimulation that were most effective may be most able to override or otherwise disrupt pathological oscillations or synchronization in the basal ganglia. Indeed, the degree of suppression of the oscillatory activity in the model neurons matched the clinical efficacy of the patterns during the finger tapping task remarkably well, suggesting that the efficacy of these patterns of DBS depended on their ability to suppress, disrupt, or otherwise regularize pathological activity in the basal ganglia.

There is evidence from many systems supporting the importance of temporal pattern in determining the effects of stimulation. Taste sensation differed across patterns of stimulation of the rat brainstem, even if the patterns had the same average frequency (Di Lorenzo et al., 2009). Temporal patterns of intra-cortical microstimulation can encode artificial tactile information in monkeys using a brain-machine-brain interface (O'Doherty et al., 2011). There is also other evidence that non-regular stimulation patterns could be more effective than regular stimulation for the treatment of movement disorders. In an adult rhesus monkey rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP), burst stimulation patterns similar to the *Absence* and *Presence* DBS patterns improved movement times relative to frequency-matched regular stimulation (Baker et al., 2011). As well, closed-loop temporally non-regular stimulation cued from physiological signals outperformed regular DBS in a MPTP primate model of PD (Rosin et al., 2011). In combination with the present findings, there is compelling evidence that non-regular temporal patterns of stimulation could be more effective than regular stimulation.

The present results highlight the importance of the temporal pattern of stimulation as a means to enhance the efficacy of DBS to treat PD. Non-regular high frequency stimulation can improve bradykinesia in patients with PD more effectively than clinically-available temporally regular stimulation, possibly by more thoroughly suppressing or disrupting pathological oscillatory activity in the basal ganglia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PD	Parkinson's disease
DBS	deep brain stimulation
GPI	internal segment of globus pallidus
STN	subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
IPG	implantable pulse generator

Highlights

- Temporal patterns of deep brain stimulation evaluated in patients with Parkinson's disease
- Stimulation patterns differentially improved motor task performance
- Three non-regular patterns of stimulation outperformed clinical regular stimulation
- Suppression of beta band power in computational model correlated with pattern efficacy
- Non-regular patterns of stimulation may improve efficacy of deep brain stimulation

Fig. 1.

Methods used to quantify the effects of different temporal patterns of DBS on motor function and neuronal activity. (A) Temporal patterns of DBS with instantaneous pulse frequency (IPF) values and ranges labeled. (B) Intraoperative experiment timeline. Each stimulation pattern was applied for four minutes with two data collection epochs. Four minutes were allowed for the effects of stimulation to wash out between stimulation patterns. Baseline data were collected before any stimulation was applied. (C) The motor task and primary measure of motor performance. Motor performance was quantified during an alternating clicking task on a two-button computer mouse using a measure of tap duration (Dur) variability (log-transformed coefficient of variation (CV) of the tap durations). (D) The structure of the computational model of the basal ganglia, which exhibited oscillatory activity in the beta frequency range.

Fig. 2. Motor Performance during different temporal patterns of DBS in persons with PD. (A) Representative data from two subjects comparing Baseline (DBS off) finger tapping to finger tapping during DBS. (B) Mean $\pm$ s.e.m. log-transformed coefficient of variation of tap durations (log CV Duration) across all stimulation conditions. Significant changes were observed across stimulation conditions (repeated measures ANOVA). Stimulation conditions that do not share the same letter are significantly different.

Fig. 3.

Correlation of motor performance during DBS with motor performance during the preceding and succeeding stimulation-off epochs. Correlation between the log CV Duration during stimulation and during the stimulation-off epochs between stimulation patterns was analyzed by calculating Pearson's correlation coefficient. (A) Motor performance during stimulation was weakly correlated with motor performance during the preceding stimulation-off period. (B) Motor performance during stimulation was significantly correlated with motor performance during the following stimulation-off period.

Fig. 4. Effects of temporal pattern of DBS on other measures of motor performance from the alternating finger tapping task. (A) Mean $\pm$ s.e.m. log-transformed coefficient of variation of the intervals between taps (log CV Interval) across stimulation conditions. (B) Mean $\pm$ s.e.m. log-transformed number of clicks per 20 s data collection epoch across stimulation conditions. While these data follow the same trend as the log CV Duration data, the differences between Baseline and stimulation-on conditions were not as pronounced, and variances were relatively large. Therefore significant differences were not observed across stimulation conditions.

Fig. 5. Specific temporal features of DBS patterns were not responsible for changes in DBS efficacy. Motor performance was analyzed to determine the effects of bursts, pauses, and irregularity in the stimulation patterns. The data were pooled across DBS patterns sharing the features of interest. Pooled log CV Duration (A), log CV Interval (B), and tapping rate (C) data from each subject are shown.

Fig. 6. Different temporal patterns of DBS differentially suppressed oscillatory activity in a computational model of the basal ganglia. (A) Spectrograms of GPI spike times from the computational model of the basal ganglia in the PD state across stimulation conditions. Log-transformed time-integral of the averaged GPI spike time peak power density in the beta frequency range (13-35 Hz; *Beta Band Power*) across stimulation conditions (B) is strongly correlated with log CV Duration (C). a.u., Arbitrary units.

Table 1

Subject Information.

Subject	Age/Sex	Hemisphere/Target Tested	Electrode Contacts ^{a,b}	AMP (V) ^b	PW (μs)	FREQ (Hz) ^b	PD medications or sedation 12 hours prior to surgery
1	54/F	Right/STN	2 -/0+ [2 -/C+]	3.5 [4.8]	90	185 [100]	none
2	59/M	Right/GPi	0 -/1 -/3+	4.0	60	185 [160]	none
3	59/M	Left/STN	2 -/3 -/0+ [2 -/3 -/C+]	2.5 [3.2]	90	185	none
4	65/M	Left/STN	0 -/1 -/2+	3.8	90	185	Midazolam (1 mg)
5	61/F	Left/STN	2 -/3+	4.5	90	185	Fentanyl (25 mcg) Dexmedetomidine (12 mcg) Clonidine (25 mcg)
6	64/F	Left/GPi	2 -/3+ [2 -/C+]	2.5 [3.5]	120	185	Carbidopa (25 mg) Levodopa (100 mg) Amantadine (100 mg)
7	59/F	Right/GPi	2 -/3+	3.5 [3.9]	120	185	none
8	66/M	Left/STN	1 -/3+	3.6	90	185 [167]	Carbidopa (25 mg) Levodopa (250 mg)
9	52/M	Left/STN	1 -/2 -/3+	4.5	90	185	Carbidopa (50 mg) Levodopa (200 mg) Ropinirole (3 mg)
10	57/M	Right/STN	1 -/2 -/3+ [1 -/2 -/C+]	3.0	90	185	none

^aQuadrupolar DBS electrode contacts are numbered 0 through 3, with 0 most distal and 3 most proximal. Contact polarity denoted by '+', '-' (anode) and '+-' (cathode) and 'C+' indicates that the IPG case was used as the anode/current return.

^bExperimental stimulation parameters are shown. Clinical settings different from the experimental settings are shown in brackets.

Abbreviations: M = male; F = female; AMP = amplitude; PW = pulse width; FREQ = frequency; STN = subthalamic nucleus; GPi = internal globus pallidus.