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Randomized, Blinded Pilot Testing of Nonconventional Stimulation Patterns and Shapes in Parkinson's Disease and Essential Tremor: Evidence for Further Evaluating Narrow and Biphasic Pulses

Umer Akbar, MD*[§]; Robert S. Raike, PhD[†]; Nawaz Hack, MD*[¶]; Christopher W. Hess, MD*; Jared Skinner, PhD*; Daniel Martinez-Ramirez, MD*; Sol DeJesus, MD*; Michael S. Okun, MD*[‡]

Objectives: Evidence suggests that nonconventional programming may improve deep brain stimulation (DBS) therapy for movement disorders. The primary objective was to assess feasibility of testing the tolerability of several nonconventional settings in Parkinson's disease (PD) and essential tremor (ET) subjects in a single office visit. Secondary objectives were to explore for potential efficacy signals and to assess the energy demand on the implantable pulse-generators (IPGs).

Materials and Methods: A custom firmware (FW) application was developed and acutely uploaded to the IPGs of eight PD and three ET subjects, allowing delivery of several nonconventional DBS settings, including narrow pulse widths, square biphasic pulses, and irregular pulse patterns. Standard clinical rating scales and several objective measures were used to compare motor outcomes with sham, clinically-optimal and nonconventional settings. Blinded and randomized testing was conducted in a traditional office setting.

Results: Overall, the nonconventional settings were well tolerated. Under these conditions it was also possible to detect clinically-relevant differences in DBS responses using clinical rating scales but not objective measures. Compared to the clinically-optimal settings, some nonconventional settings appeared to offer similar benefit (e.g., narrow pulse widths) and others lesser benefit. Moreover, the results suggest that square biphasic pulses may deliver greater benefit. No unexpected IPG efficiency disadvantages were associated with delivering nonconventional settings.

Conclusions: It is feasible to acutely screen nonconventional DBS settings using controlled study designs in traditional office settings. Simple IPG FW upgrades may provide more DBS programming options for optimizing therapy. Potential advantages of narrow and biphasic pulses deserve follow up.

Keywords: Biphasic pulses, deep brain stimulation, essential tremor, irregular patterns, narrow pulse width, Parkinson's disease

Address correspondence to: Michael S. Okun, MD, Center for Movement Disorders and Neurorestoration, University of Florida, 3450 Hull Rd, Gainesville, FL, 32607, USA. Email: okun@neurology.ufl.edu

* University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, FL, USA;
† Neuromodulation Global Research, Medtronic Inc., Minneapolis, MN, USA;
‡ Departments of Neurology and Neurosurgery, University of Florida, Gainesville, FL, USA;
§ Department of Neurology, Brown University, Providence, RI, USA; and
¶ US Naval Hospital, Okinawa, Japan

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INTRODUCTION

Deep brain stimulation (DBS) can be an effective surgical therapy for select patients with medication-refractory symptoms of movement disorders, including Parkinson's disease (PD) (1), essential tremor (ET) (2), and dystonia (3). FDA-approved DBS therapies for movement disorders involve implantation of electrodes into the ventral intermedius nucleus (VIM) for medication refractory ET, and either the globus pallidus internus (GPi) or the subthalamic nucleus (STN) for PD, depending on the patient's disabling features and the results of an interdisciplinary evaluation. The DBS lead is connected to an implantable pulse-generator (IPG), which conventionally delivers charge-balanced, square, cathodic pulses with specific amplitudes and durations at continuous frequencies. The optimization of IPG programming for DBS is most often conducted in the in-office setting at regular intervals.

DBS can be programmed to address specific patient symptoms, including tremor and rigidity. DBS can also be adjusted according to the specific medication side effects such as dyskinesia. DBS therapy for movement disorders is typically delivered at high frequencies ($>$100 Hz) (4,5), although DBS at $<$100 Hz may also be beneficial in a subset of PD and dystonia patients (6–10). Pulse widths for PD and ET therapies typically range from 60 to 120 μs (2,4,11), whereas those for dystonia tend to be longer (120 to $>$200 μs) (12–15). Therapy customization may also involve changes to the location and shape of the stimulation field along the DBS lead (16,17). However, in some cases the therapeutic window of DBS may be unacceptably narrow possibly due to suboptimal lead placement or other unidentified factors (18–21). In these cases there remains a critical need for additional approaches for optimizing the therapy.

The high energy consumption of neurostimulation therapies such as DBS is also a challenge. Even with clinically-optimal DBS, IPGs with primary cell batteries require replacement approximately every 2–5 years, depending on the stimulation parameters. Not surprisingly, higher DBS pulse amplitudes, longer pulse widths, and higher frequencies drain the battery more rapidly. Use of multiple DBS contact cathodes to shape the stimulation field also results in greater battery drain. Although IPGs with rechargeable batteries are currently available, replacement may still be required approximately every 7–9 years. In addition, increased battery consumption carries the distinct disadvantage of shortened recharge intervals with rechargeable IPGs. Therefore, there is also an obvious interest in developing more energy-efficient DBS therapy delivery modalities. There is emerging evidence that some nonconventional approaches to DBS programming may improve both therapy efficacy and efficiency. For example, several studies suggest that more narrow DBS pulse widths than conventionally used may both reduce energy consumption and widen the therapeutic window (4,5,11). In fact, a recent pilot study found that DBS pulse widths even more narrow than commercially available (20–40 μs) may offer further improvements (22). Findings from several preclinical and clinical studies also suggest that some irregular DBS pulse patterns may improve motor symptoms more effectively and efficiently (23–29). Furthermore, a number of computer modeling studies exploring alternative DBS pulse shapes suggest similar advantages (30–32).

Although the overall implication is that standard DBS can be optimized with nonconventional programming, more rigorous evaluations in chronically-implanted subjects under real-world conditions are needed. In general, there is a critical need for more well-designed exploratory and feasibility studies of potential central nervous system therapeutics, as their underutilization is likely a key contributor to the frequent failure of later-phase and pivotal trials (33). Designing well-controlled exploratory and feasibility investigations of DBS therapy for movement disorders is especially challenging, but may be accomplished with creative and novel approaches (34,35). Therefore, in the current study we assessed whether it was feasible to conduct controlled-testing of several nonconventional DBS settings in chronically-implanted PD and ET patients in a traditional in-office setting.

MATERIALS AND METHODS

Study Design and Subjects

Others have successfully implemented blinded, randomized study designs for assessing the clinical effects of nonconventional DBS concepts in small to moderate samples ($n < 10$–20) of movement disorder patients (24–26,29,35). The primary objective of this study was to determine if a similar approach could be taken for testing the tolerability of several nonconventional DBS settings in PD ($n = 8$) and ET ($n = 3$) patients over the course of 2–3 hours in a single office visit. Tolerability was defined as lack of intolerable side effects that would lead to discontinuation of the nonconventional stimulation-settings. To accommodate the study schedule, approximate 2 min DBS wash-in and wash-out periods were used; similar periods have been demonstrated to be appropriate in prior studies (24,26–32,36) conducted in chronically-implanted patients. All subjects were blinded to the stimulation settings and to whether stimulation was on or off, although they were made aware that the settings had changed. All settings were tested in a pseudorandom order in the same environment as where traditional IPG programming occurs. Motor assessments were videotaped, and independent ratings were collected by three raters: one unblinded rater, one blinded rater present during testing, and one blinded rater via video recordings (with the exception of PD rigidity, which cannot be assessed via video). Subjects were instructed to report any side effects during the course of the study, including pulling (contractions), tingling, blurry vision, double vision, speech changes, or walking problems. All subjects were assessed in the off-medication state, as all antitremor and dopaminergic medications were withheld for at least 12 hours. All procedures were reviewed and approved by the University of Florida Internal Review Board.

Subjects were recruited during routine DBS programming sessions at the University of Florida Health Center for Movement Disorders and Neurorestoration. Since our study was designed to test these nonconventional settings acutely, we included disorders in which acute changes with stimulation alterations are more apparent (e.g., PD and ET vs. dystonia). Inclusion criteria were: (1) PD or ET diagnosis by a fellowship-trained movement disorder neurologist using strict criteria (37), (2) implanted with DBS, and (3) optimized on DBS settings with a minimum of four monthly clinical programming sessions. Exclusion criteria were: (1) diagnosis of another neurodegenerative disorder, (2) multiple DBS surgeries performed due to infection, revision, or other complication, (3) DBS settings not optimized, (4) fewer than four DBS outpatient programming sessions, and (5) suboptimally placed DBS lead as revealed by postoperative imaging. For subjects with bilateral DBS implants, DBS was turned off on the side not being tested for the duration of the study.

Nonconventional DBS Settings

The nonconventional DBS settings were delivered using a custom temporary downloadable firmware (FW) that was developed to be compatible with Medtronic Activa PC, SC, and RC IPGs (Medtronic,

Table 1. The protocol was for each subject to experience a total of 11 DBS settings.

Testing order	DBS parameters tested	Assessments performed?
1	Clinically-optimal settings (*ClinDBS*)	Yes
2	Stimulation turned off (*DBS-off*)	Yes
Random	Biphasic pulses (*BiphClinV*)	Yes
–	Stimulation turned off (Washout)	No
Random	Biphasic pulses at 70% amplitude (*Biph70%V*)	Yes
–	Stimulation turned off (Washout)	No
Random	Irregular patterns (*20%CVClinV*)	Yes
–	Stimulation turned off (Washout)	No
Random	Irregular patterns at 70% amplitude (*20%CV70%V*)	Yes
–	Stimulation turned off (Washout)	No
Random	50% shorter pulse widths (*50%PWClinV*)	Yes
–	Stimulation turned off (Washout)	No
Random	50% shorter pulse widths at 150% amplitude (*50%PW150%V*)	Yes
10	Stimulation turned off (*DBS-off*)	Yes
Random	Clinically-optimal settings at 70% amplitude (*70%ClinV*)	Yes
11	Clinically-optimal settings (*ClinDBS*)	Yes

Clinically-optimal settings and off-stimulation were both tested at the beginning and end of the study. All other settings were tested in random order. Subjects were blinded to all settings and were only aware of a change.

Neuromodulation, Minneapolis, MN; 38,39) and controlled by a trained neurologist using a Microsoft Windows-based user interface running on a standard PC laptop that was connected to a telemetry head (Medtronic, Neuromodulation). All stimulation settings included charge-balanced pulses at or below standard clinical amplitudes and within all FDA safety guidelines (30 $\mu C/cm^2$/phase). The research system allowed stimulation with nonconventional settings to be immediately stopped at the request of the subject in case of discomfort or at any time deemed appropriate by the attending neurologist. The temporary FW was removed from all subjects' IPGs at the conclusion of the study, and all patients were returned to their clinically-optimal therapeutic settings.

Subjects were tested under 11 total DBS settings (Table 1). To control for fatigue and order effects of the different settings, subjects were evaluated under their clinically-optimal settings (*ClinDBS*) and with stimulation turned off (*DBS-off*) both at the beginning and then end of the study (i.e., two assessments for each). Due to technical limitations of the research system, the optimal stimulation frequency was sometimes required to be adjusted slightly but remained constant throughout the study (e.g., 185 Hz was changed to 190 Hz; see Results section). Whereas standard DBS pulses were charge balanced with a passive recharge (Fig. 1a, left), nonconventional charge-balanced biphasic pulses with a square-wave active recharge were tested at the clinically-optimal voltage (*BiphClinV*; Fig. 1a, right). Using the research platform, the IPG was capable of delivering pulse widths as low as 10 μs (Fig. 1b), and it was used to deliver pulse widths 50% shorter than clinically-optimal at the clinically-optimal voltage (*50%PWClinV*). Irregular patterns of stimulation consisting of the same average stimulation frequency as the clinically-optimal settings but with an overall 20% coefficient of variance were tested at the clinically-optimal voltage (*20%CVClinV*; Fig. 1c). Because one objective of the study was to explore the feasibility of assessing the therapeutic efficiency of different DBS settings, the biphasic pulses and the irregular patterns were also tested at an arbitrarily reduced voltage (*Biph70%V* and *20%CV70%V*). To control for the effect of low voltage, the clinically-optimal frequency and pulse width was also tested at the reduced voltage (*70%ClinV*). Conversely, the 50% shorter pulse widths were also tested at an increased voltage (*50%PW150%V*) but with a similar energy consumption profile overall (see Fig. 3).

Motor Assessments

A secondary objective of the study was to explore for potential efficacy signals associated with the nonconventional settings. To do so, part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was used for evaluating the PD motor symptoms and the Fahn–Tolosa–Marin tremor rating scale was used for evaluating ET motor symptoms contralateral to the site of stimulation. An accelerometer was also used for scoring rest tremor, postural tremor, and action tremor during finger tapping on a scale of 0–4 corresponding to tremor severity using algorithms previously validated by the manufacturer (Kinesia, Great Lakes NeuroTechnologies, Cleveland, OH) (40,41). Tremor was measured for approximately 10 sec at rest, for 10 sec with arms held outstretched in front of the body. Bradykinesia was then measured more than ten finger taps. Gait was assessed using the Timed-up-and-go (TUG) test (42) and the GaitRite walkway and software suite (GaitRite CIR Systems Inc., Havertown, PA) (43,44).

Energy Consumption Comparisons

Another secondary objective of the study was to assess the energy demand on a commercial IPG of delivering the nonconventional DBS settings. To do so IPG battery current drain associated with each DBS setting was estimated in a bench-top setting using either an Activa SC or an Activa PC IPG, depending on the subject (see case series Supporting Information). The IPG circuit board was exposed and connected to a model E3631A power supply (Agilent, Santa Clara, CA) set to 3 V and a model 2001 digital multimeter set to DC mode (Keithley, Cleveland, OH). The IPG header was connected to a DBS lead (3389, Medtronic Neuromodulation) modified at the distal end with a pair of brass pins connected to electrode channels 2 and 3. For testing bipolar electrode configurations, a model TDS460A oscilloscope (Tektronix, Beaverton, OR) was connected to both pins with wiring. For testing monopolar electrode configurations, the oscilloscope was connected to the pin corresponding to electrode 3 and a ground wire that was clipped to the IPG case. In all cases a 500 Ω

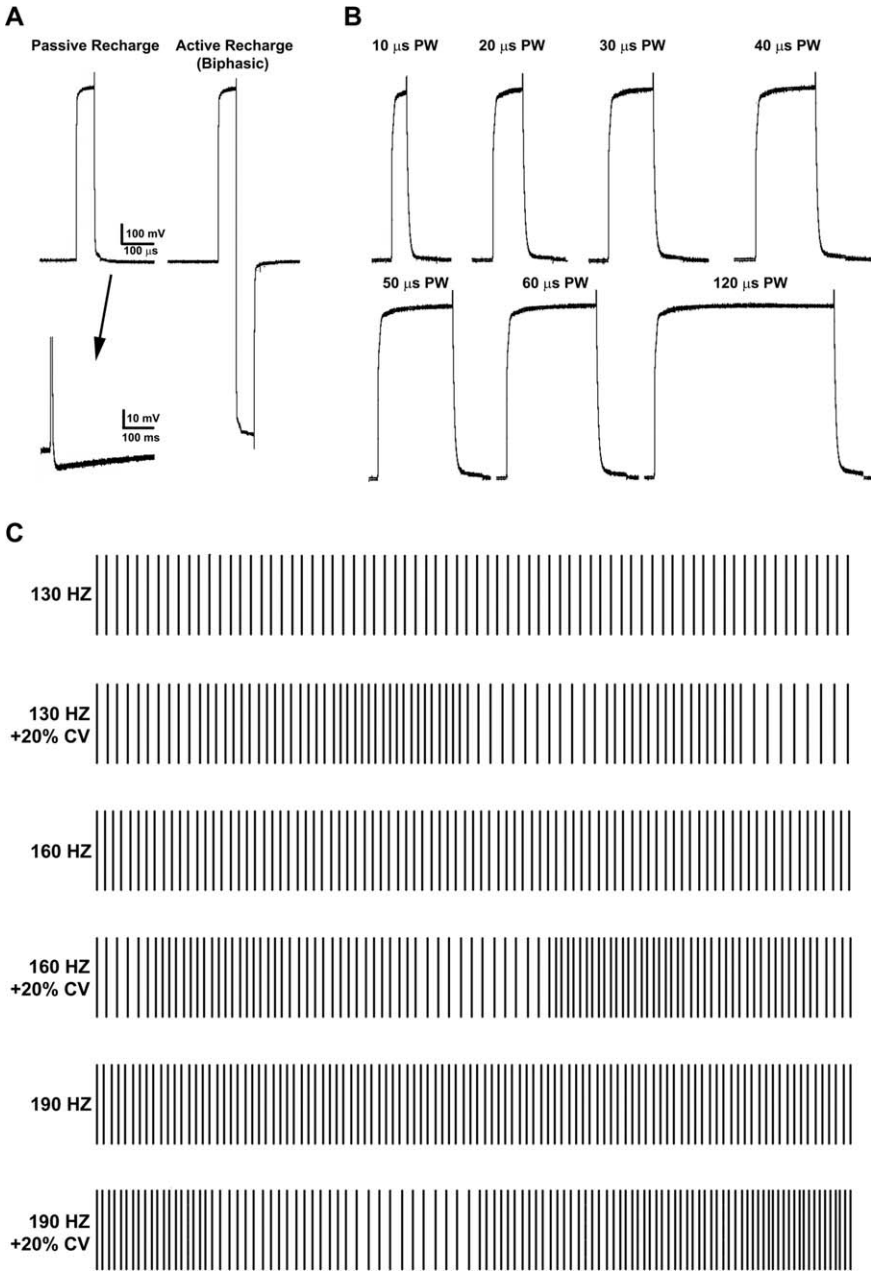

Figure 1. Standard DBS devices deliver change-balanced pulses with a passive recharge (a, left, arrow). The research programmer system was used to deliver biphasic pulses which were charge balanced with a square-wave active recharge (a, right). The research system was capable of delivering pulse widths as low as 10 μs. Standard DBS devices deliver change-balanced pulses with a passive recharge (a, left, arrow) (b), and was used to deliver pulse widths 50% shorter than the clinically-optimal settings. The research system was also used to deliver irregular patterns of stimulation (c), which were the same average stimulation frequency as the clinically-optimal settings but exhibited an overall 20% coefficient of variance (CV).

resistor load was included. The multimeter was configured to display a moving average of current drain, which was recorded for each DBS setting after approximately 1 min of testing (Fig. 3).

Data Analysis

To explore for an efficacy signal, PD motor outcomes associated with the nonconventional DBS settings were compared to those associated with the *ClinDBS* condition. The data were expressed in box and whisker plots as the median outcome delta relative to the median value with the *ClinDBS*, whereby the box represents the inter-quartile range, the whiskers represent the spread, the line represents the median and the dots represent outliers (Fig. 2). There was no statistically significant difference between the UPDRS III scores when including ratings from all three neurologists and those with the unblinded neurologist removed (not shown). Therefore, median UPDRS-III scores from individual subjects were calculated from the assessments by the three neurologists, except for subject PD1, who was assessed by only the two on-site neurologists due to video equipment malfunction. The UPDRS-III, TUG, PEG, and Gait Rite values with ClinDBS and DBS-off expressed were calculated from the median of the assessments taken at the beginning and at end of testing. Because not all of the PD subjects were tested during each DBS setting, the sample sizes expressed range from $n = 5–7$. The nonparametric Wilcoxon–Mann–Whitney *U*-test was used to

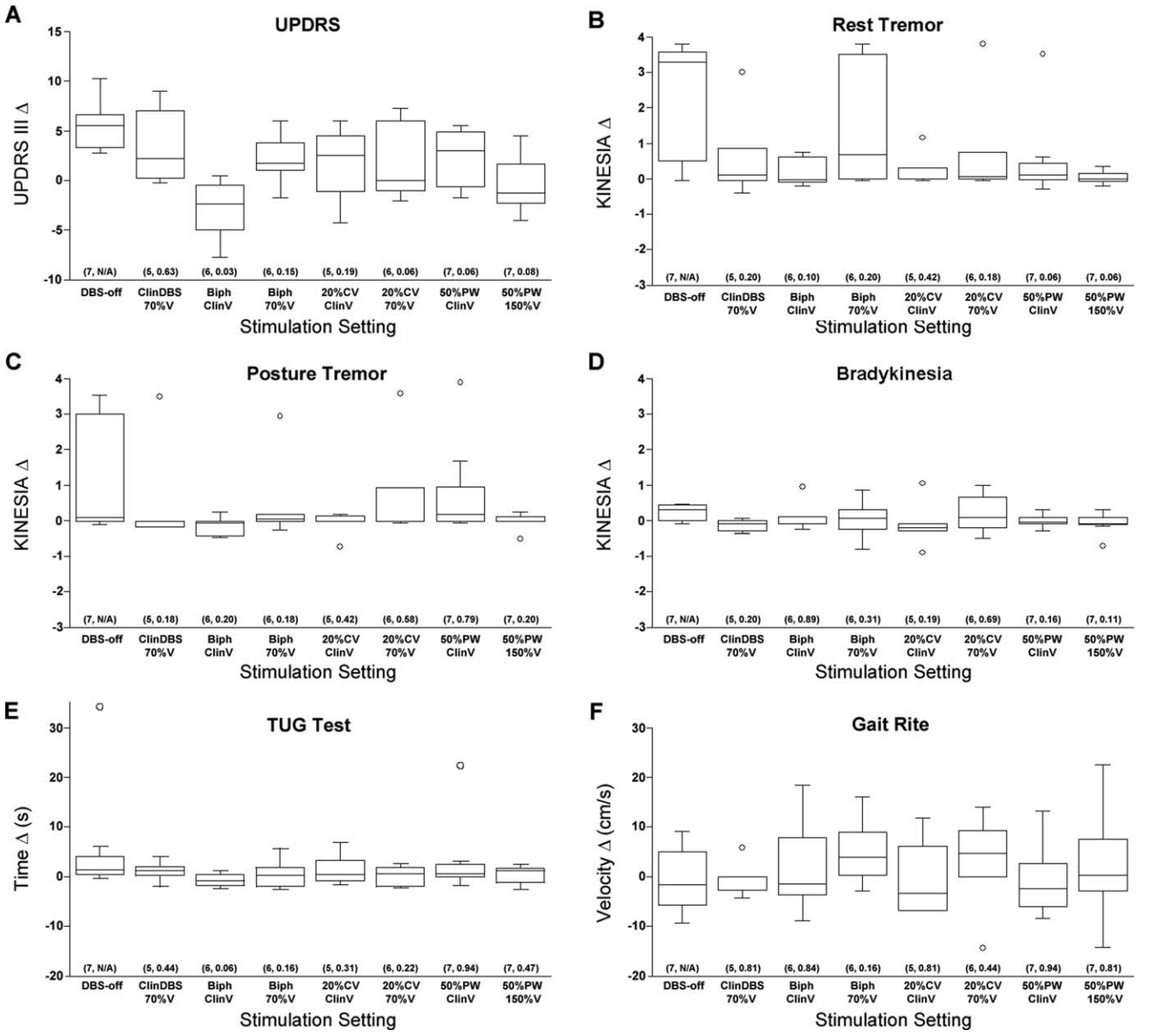

Figure 2. Grouped PD UPDRS-III (a), Kinesia (b–d), TUG (e), and Gait Rite (f) data expressed as the median delta relative to the median value during clinical DBS. The box represents the inter-quartile range, the whiskers represent the spread, the line represents the median and the dots represent outliers. Data were analyzed in pairs using the nonparametric Wilcoxon-Mann-Whitney *U*-test, comparing the median delta during DBS OFF to the median deltas during the nonconventional DBS settings. Sample sizes ranged from $n = 5–7$ because not all of the PD subjects were tested during each nonconventional setting. Sample sizes and approximated *p* values are listed at the bottom of each box (*n*, *p*).

test for pairwise statistical differences within the PD cohort to avoid assumptions of normality and to compensate for the small and unequal sample sizes. Therefore in cases when DBS settings were not tested because of subject dropout, setting intolerability or equipment malfunction, the analyses included data pairs only from subjects who completed the testing. Individual median PD and ET motor outcome values are presented Table 2 (median outcome values for ET subjects were calculated as described above for PD). Given the small number of patients and variable data size, we did not correct for multiple comparisons. The results of this study should be used to guide the design of future statistically-powered studies.

To compare the relative energy efficiency of the nonconventional DBS settings, IPG current drain data are expressed as mean values ± SEM and analyzed using a paired Students *t*-test, comparing the current drain with clinically-optimal DBS settings delivered using the commercial IPG FW (cFW) to the current drain with each nonconventional setting (Fig. 3).

RESULTS

Tolerability of Nonconventional DBS Settings

Eleven consecutive subjects were enrolled in the study (n = eight PD and three ET). Overall mean age was 62 years (range 47–75 years). Mean disease duration for PD subjects was 11 years (range 8–18 years) and for ET subjects was 20 years (range 6–40 years). In all but one of the PD cohort, STN was the surgical target; GPi was the surgical target for subject PD4. VIM was the surgical target for all ET subjects. All implanted electrodes were 3387 model (Medtronic, Neuromodulation, Minneapolis, MN, USA). Only two subjects

terminated the study prior to completing the full protocol. Subject PD3 withdrew from the study after completing 8 of the 11 DBS settings because of general fatigue. Subject PD4 withdrew from the study after completing only three of the settings due to off-medication fatigue. In addition, testing could not be completed in two subjects because of intolerable side effects. For subject PD6, intolerable settings included *BiphClinV* (lip pulling and speaking difficulties), *20%CVClinV* (phosphenes), and *70%ClinV* (phosphenes). For subject PD8, *BiphClinV* was the only intolerable setting (dizziness and blurred vision). All other subjects were able to complete the full clinical protocol and accompanying motor assessments. Overall, the proportion of subjects who responded better to the nonconventional settings (i.e., the responder rate) was 1/5 for *70%ClinV*, 6/6 for *BiphClinV*, 1/6 for *70%BiphClinV*, 2/5 for *20%CVClinV*, 2/6 for *20%CV70%V*, and 3/7 for both *50%PWClinV* and 50%*PW150%V*. In general, motor symptoms appeared discernably better with any of the active settings compared to the *DBS-off* (sham) condition. Overall, no unexpected adverse events occurred and the nonconventional DBS settings were well tolerated, although in some cases mild side effects were experienced. See Tables 2 and 3 and the cases series Supporting Information for individual details and results.

PD Motor Assessments

Although the primary objective of this pilot study was to determine the feasibility of acutely testing the tolerability of several nonconventional DBS settings, we also explored for any potential efficacy signals in the PD cohort. To do so, first we tested whether a clinically-relevant UPDRS-III difference could even be detected under these conditions in the PD subjects that were able to complete the study from beginning to end (i.e., even if some settings were intolerable; $n = 6$). As expected, median UPDRS-III scores with *DBS-off* was significantly worse compared to that with *ClinDBS* (35.6 vs. 28.9; $p = 0.03$). In contrast, while median UPDRS-III score with *ClinDBS* trended upward from the beginning to the end of the study, the difference was not statistically significant (25.5 vs. 31.6; $p = 0.44$). Similarly, no significant difference was detected in the median UPDRS-III score with *DBS-off* between the beginning and end of the study (33.8 vs. 35.6; $p = 0.41$), indicating that fatigue was not likely a major factor in the infrequent intolerability of some nonconventional DBS settings described above or other outcomes described below. Overall, these results demonstrate that the testing conditions were sufficient to detect potential differences in DBS therapeutic efficacy between different DBS settings using standard clinical rating scales in this case on vs. off stimulation.

Next we assessed if there was a potential efficacy advantage associated with any of the nonconventional DBS settings. To do so, the UPDRS-III scores were plotted as a delta relative to the scores with *ClinDBS* (Fig. 2a). Consistent with the results above, the median UPDRS-III score delta with *DBS-off* was $\sim$5 points greater than with *ClinDBS*. As expected, the UPDRS-III score deltas with *70%ClinV* were also generally $>$0, or suboptimal relative to *ClinDBS*. Conversely, the median UPDRS-III score deltas from *ClinDBS* varied with the nonconventional settings, as some of the nonconventional settings appeared to offer similar benefit and others lesser benefit. Interestingly, the median UPDRS-III score delta with *BiphClinV* was $\sim$2.5 points less than with *ClinDBS*, suggesting that this setting delivered greater benefit than *ClinDBS*. Pairwise statistical tests were then conducted to detect differences between these UPDRS-III score deltas and those with *DBS-off*, including data only from subjects who completed the testing for the nonconventional setting ($n = 5$–7 total per condition; see Methods section). Whereas the median UPDRS-III score deltas with *20%CV70%V*, *50%PWClinV* and 50%*PW150%V* tended to be lower than with *DBS-off* ($p = 0.06$–0.08), only the median UPDRS-III delta with *BiphClinV* was significantly lower than with *DBS-off* ($p = 0.03$). Taken together, these results suggest that DBS delivered with the nonconventional biphasic pulse may offer efficacy advantages over standard therapy, although follow-up studies specifically designed for testing this concept will be required to confirm.

In the PD subjects that completed the study from beginning to end no significant differences were detected in the median Kinesia, TUG or GaitRite values with *ClinDBS* between the beginning and end of the study ($n = 5$–6; $p = 0.17$–1.0). No significant differences were detected in the median Kinesia, TUG or GaitRite values with *DBS-off* at the beginning and end of the study ($p = 0.20$–0.41). Although some of the outcomes of these assessments were positive within individual subjects (Table 2), there were no statistically significant differences detected in the median Kinesia, TUG or GaitRite values between *DBS-off* and *ClinDBS* ($p = 0.06$–0.86), although the Kinesia rest tremor scores trended lower with *ClinDBS* ($p = 0.06$). Plots comparing the median deltas of these different assessments relative to *ClinDBS* provide insight (Fig. 2b–f). For example, the median Kinesia rest and postural tremor score deltas varied considerably with *DBS-off* (Fig. 2b,c), but were approximately 0 with most of the nonconventional settings. Conversely, the median GaitRite velocity deltas were inconsistent across all settings, whereas median TUG time deltas were relatively static regardless of setting. Moreover, the group-wise outcomes of these objective assessments were likely influenced by the clinical spectrum of the subjects and the applicability of the different assessments under these specific testing conditions. These results can be used as design inputs to follow-up studies incorporating objective motor assessments.

ET Motor Assessments

Three ET subjects were tested (two females), and in most cases the nonconventional settings appeared to be more effective compared to DBS-off (see Table 2). Specifically, the *BiphClinV*, *20%CVClinV*, and *70%ClinV* settings appeared to achieve similar benefits as with ClinDBS settings. Overall, all of the nonconventional settings were well-tolerated. See Table 2 and the cases series Supporting Information for individual details and results.

Energy Consumption of Nonconventional DBS Settings

The impact on the IPG battery of delivering nonconventional DBS settings may not be straightforward and is an important consideration when proposing alternative programming paradigms. To determine whether delivering any of the nonconventional DBS settings may be associated with unexpected changes in the energy efficiency of the IPG, the amount of current drained from the battery was estimated with each of the nine DBS settings for all 11 study subjects (Fig. 3). Average current drain per minute with each setting delivered using the research FW was compared to the average current drain with the *ClinDBS* settings delivered using the commercial FW (cFW). The average current drain with the *ClinDBS* was nearly identical with the cFW and rFW (101.34 ± 8.89 μA vs. 96.11 ± 7.69 μA; $p = 0.17$). As expected, the current drain was significantly less with the IPG turned on but with *DBS-off* (54.47 ± 1.92 μA; $p < 0.0001$). Also not surprisingly, reducing stimulation output with a 30% decrease in amplitude or a 50% decrease in the pulse width (*70%ClinV* and *50%PWClinV*) was also associated with significant less current drain (78.24 ± 7.69 μA and 73.09 ± 4.52 μA; $p < 0.001$ and 0.0001). There was no significant difference in current drain

Table 2. Individual subject results.

	UPDRS-III scores									Kinesia scores			PEG test	TUG test	Gait rite
Subject	UE rest tremor	UE action/ postural tremor	LE rest tremor	Finger tapping speed	UE rigidity	LE rigidity	Neck rigidity	Gait	Total UPDRS-III score	UE rest tremor	UE postural tremor	UE finger-tapping	Time (s)	Time (s)	Speed (cm/s)
PD1 (L STN, 2^{-} C^{+}, 2.6 V, 110 μs, 190 Hz)															
Clinical DBS	0	0	0	2.25	1.75	2.0	2.25	1.5	31.0	0.05	0	2.5	–	11.2	133.2
DBS OFF	0.25	0	0	3.0	1.75	2.0	2.75	1.5	34.25	0	0	2.8	–	45.6	124.2
Clinical DBS, 70% amplitude	0	0	0	3.0	2.0	2.5	3.0	1.5	38.0	0	0	2.4	–	13.3	128.9
Biphasic	0	0	0	2.5	1.5	2.0	2.0	1.5	30.5	0	0	–	–	10.4	141.0
Biphasic, 70% amplitude	0	0	0	2.5	1.5	2.0	2.0	1.5	32.0	0	0	1.7	–	10.0	137.0
20% CV	0	0	0	3.0	1.5	2.0	2.5	2.0	35.5	0	0	2.2	–	14.7	105.6
20% CV, 70% amplitude	0	0	0	2.5	2.0	2.5	3.0	1.5	37.0	0	0	2.0	–	12.2	134.9
50% PW	0	0	0	2.5	2.5	2.5	3.0	1.5	36.5	0	0	2.2	–	11.6	138.3
50% PW, 150% amplitude	0	0	0	2.5	1.0	2.0	2.5	1.5	33.0	0	0	1.8	–	11.3	132.9
PD2 (L STN, 1^{-} C^{+}, 3.0 V, 90 μs, 190 Hz)															
Clinical DBS	0	0	0	2.5	1.5	1.5	1.75	1.0	37.09	0	0	0.45	–	9.8	131.8
DBS OFF	0	0.5	0	2.75	1.75	1.5	2.0	1.0	40.5	0	0	0.9	–	10.9	129.4
Clinical DBS, 70% amplitude	0	0	0	3.0	2.0	1.5	2.0	1.0	46.0	0.1	0	0.1	–	10.5	129.1
Biphasic	0	0	0	2.0	1.0	1.5	2.0	1.0	42.0	0	0	0.2	–	10.5	128.1
Biphasic, 70% amplitude	0	1.0	0	2.5	1.0	1.5	1.5	1.0	40.0	0	0	1.3	–	10.8	135.9
20% CV	0	0	0	3.0	1.0	1.5	2.0	1.0	43.0	0	0	0.5	–	11.5	125.0
20% CV, 70% amplitude	0	0	0	2.0	2.0	1.5	2.0	1.0	39.0	0	0	1.1	–	10.3	131.8
50% PW	0	1.0	0	3.0	1.5	1.5	2.0	1.0	43.0	0.1	0	0.4	–	11.4	123.4
50% PW, 150% amplitude	0	0	0	2.0	2.0	1.5	1.5	1.0	43.0	0	0	0.3	–	11.1	126.4
PD3 (L STN, 2^{-} C^{+}, 2.5 V, 90 μs, 160 Hz)															
Clinical DBS	1.0	1.0	0	2.0	2.0	1.0	1.5	1.0	42.5	0.1	1.0	1.5	–	8.5	137.8
DBS OFF	3.0	2.0	1.0	3.0	2.5	1.5	2.0	1.0	48.0	3.4	4.0	1.5	–	8.9	128.5
Clinical DBS, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–		
Biphasic	0	1.0	0	2.0	2.0	0.5	1.5	1.0	43.0	0.7	0.6	1.6	–	8.5	128.9
Biphasic, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–		
20% CV	0	2.0	0	2.0	2.0	1.0	1.5	1.0	45.0	0.4	0.3	1.6	–	8.8	134.5
20% CV, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–		
50% PW	2.0	2.0	0	2.0	2.0	1.5	2.0	1.0	48.0	0.7	2.7	1.7	–	8.5	130.1
50% PW, 150% amplitude	2.0	1.0	0	2.0	2.5	1.0	2.0	1.0	47.0	0.4	0.5	1.4	–	9.3	123.5

Table 2. *Continued*

	UPDRS-III scores									Kinesia scores			PEG test	TUG test	Gait rite
Subject	UE rest tremor	UE action/ postural tremor	LE rest tremor	Finger tapping speed	UE rigidity	LE rigidity	Neck rigidity	Gait	Total UPDRS-III score	UE rest tremor	UE postural tremor	UE finger-tapping	Time (s)	Time (s)	Speed (cm/s)
PD4 (L GPi, 1^{-} 2^{+}, 3.2 V, 90 μs, 130 Hz)															
Clinical DBS	0	0	0	3.0	2.0	1.5	1.5	2.0	40.0	–	–	–	–	–	–
DBS OFF	0	0	0	2.0	2.5	1.5	2.0	2.0	39.0	–	–	–	–	–	–
Clinical DBS, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Biphasic	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Biphasic, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
20% CV	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
20% CV, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
50% PW	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
50% PW, 150% amplitude	0	0	0	2.0	2.5	1.5	2.5	2.0	42.0	–	–	–	–	–	–
PD5 (L STN, 1^{-} 3^{+}, 2.0 V, 120 μs, 190 Hz)															
Clinical DBS	0	0.5	0	1.5	2.25	2.25	2.0	1.0	33.0	0.2	0.1	1.0	–	9.8	111.4
DBS OFF	3.5	3.0	0.5	1.5	2.5	2.75	2.25	1.0	40.0	4.0	3.65	1.45	–	10.5	120.6
Clinical DBS, 70% amplitude	3.0	2.0	0	2.0	2.0	2.5	2.0	1.0	36.0	3.2	3.6	0.7	–	9.9	117.3
Biphasic	0	0	0	1.0	1.5	2.5	1.5	1.0	28.0	0	0	1.1	–	9.2	129.9
Biphasic, 70% amplitude	4.0	1.0	0	1.5	2.5	2.5	2.0	0	39.0	4.0	0.3	1.3	–	9.3	127.4
20% CV	0	0	0	1.5	2.0	2.5	1.5	1.0	39.0	0.2	0.3	0.8	–	9.4	123.2
20% CV, 70% amplitude	4.0	3.0	1.0	1.5	2.5	2.0	2.0	1.0	32.0	4.0	3.7	1.1	–	10.1	125.4
50% PW	3.0	0	0	1.5	2.5	2.5	2.0	1.0	36.0	3.7	4.0	0.9	–	10.0	124.6
50% PW, 150% amplitude	0	0	0	1.0	1.5	2.5	1.5	1.0	29.0	0.1	0.1	1.1	–	10.4	117.4
PD6 (R STN, 2^{-} C^{+}, 2.5 V, 150 μs, 130 Hz)															
Clinical DBS	0	0.5	0	1.5	0.75	0.5	0.75	2.0	26.75	0	0.2	1.1	38.8	18.5	52.9
DBS OFF	2.5	1.0	0	2.0	1.5	0.75	1.0	2.0	37.0	3.65	0.3	1.5	57.4	21.6	56.4
Clinical DBS, 70% amplitude	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Biphasic	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Biphasic, 70% amplitude	0	1.0	0	1.0	1.0	0.5	1.0	2.0	28.0	0	0.3	1.3	51.2	21.5	50.1
20% CV	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
20% CV, 70% amplitude	0	1.0	0	3.0	1.5	0.5	1.0	2.0	34.0	0	0.2	2.1	37.7	17.4	38.6
50% PW	0	1.0	0	2.0	2.0	0.5	1.0	2.0	31.0	0	0.4	1.4	48.1	29.7	50.5
50% PW, 150% amplitude	0	1.0	0	2.0	1.5	0.5	1.0	1.0	28.0	0	0.3	1.4	44.8	17.4	75.4

Table 2. *Continued*

	UPDRS-III scores									Kinesia scores			PEG test	TUG test	Gait rite
Subject	UE rest tremor	UE action/ postural tremor	LE rest tremor	Finger tapping speed	UE rigidity	LE rigidity	Neck rigidity	Gait	Total UPDRS-III score	UE rest tremor	UE postural tremor	UE finger-tapping	Time (s)	Time (s)	Speed (cm/s)
PD7 (R STN, 2^{-} C^{+}, 1.5 V, 90 μs, 130 Hz)															
Clinical DBS	0.5	1.0	0	1.0	2.0	1.0	1.0	0	24.25	0.15	0.65	1.1	38.7	9.3	134.6
DBS OFF	0.5	1.0	0	1.5	2.0	1.0	1.0	0	27.0	1.15	0.55	1.1	38.2	9.1	141.0
Clinical DBS, 70% amplitude	1.0	0	0	2.0	1.0	1.0	1.0	0	24.0	1	0.5	1.1	36.1	8.4	131.9
Biphasic	0	0	0	1.0	2.0	1.0	1.0	0	21.0	0.9	0.9	1.0	36.3	8.2	133.9
Biphasic, 70% amplitude	1.0	1.0	0	1.0	2.0	1.0	1.0	0	28.0	1.5	0.4	1.0	40.3	8.4	143.5
20% CV	0	0	0	1.0	1.0	1.0	1.0	0	20.0	1.3	0.8	1.0	45.8	8.6	140.7
20% CV, 70% amplitude	0	0	0	1.0	2.0	1.0	1.0	0	24.0	0.9	0.6	0.9	41.5	8.4	143.9
50% PW	0	1.0	0	1.0	2.0	1.0	1.0	0	23.0	0.4	0.9	1.0	37.9	8.5	130.1
50% PW, 150% amplitude	0	0	0	1.0	2.0	1.0	1.0	0	23.0	0.5	0.9	1.0	35.9	8.1	143.6
PD8 (R STN, 1^{-} C^{+}, 2.5 V, 90 μs, 190 Hz)															
Clinical DBS	0	0.5	2.0	1.0	1.25	0	0.5	0	12.75	0.5	0.45	0.75	39.6	9.0	125.3
DBS OFF	2.5	2.0	2.0	1.5	1.5	0	0.5	0	19.0	4.0	3.5	0.65	40.2	9.2	123.6
Clinical DBS, 70% amplitude	0	1.0	2.0	1.0	1.5	0	0.5	0	15.0	0.1	0.3	0.8	40.5	10.2	125.3
Biphasic	0	0	1.0	0	0.5	0	0.5	0	5.0	0.4	0	0.7	33.4	9.3	123.1
Biphasic, 70% amplitude	3.0	2.0	2.0	1.0	1.0	0	0.5	0	15.0	4.0	3.4	0.5	41.5	9.9	125.6
20% CV	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
20% CV, 70% amplitude	0	2.0	2.0	1.0	1.0	0	0.5	0	13.0	0.6	1.4	0.7	37.0	10.5	132.8
50% PW	0	1.0	2.0	1.0	1.5	0	0.5	0	11.0	0.2	0.4	0.7	39.1	10.0	125.6
50% PW, 150% amplitude	0	0	1.0	1.0	1.0	0	0.5	0	10.0	0.3	0.6	0.8	39.1	10.0	125.6

Table 2. *Continued*

							TRS scores				Kinesia scores		PEG test	TUG test	Gait rite
Subject	UE rest tremor	UE postural tremor	UE action tremor	LE rest tremor	LE postural tremor	UE action tremor	Drawing A + B + C	Writing	Pouring	Total score	UE rest tremor	UE postural tremor	Time (s)	Time (s)	Time (s)
ET1 (R ViM, 2^{-} C^{+}, 1.0 V, 90 μs, 130 Hz)															
Clinical DBS	0	0	0	0	0	0	1.0	2.0	0.5	7.5	0	0	–	11.2	115.2
DBS OFF	0	0.5	1.0	0	0	0	4.0	2.0	0.5	12.0	0	0.05	–	10.8	113.3
Clinical DBS, 70% amplitude	0	0	0	0	0	0	2.0	2.0	0	6.0	0	0	–	9.6	117.0
Biphasic	0	0	0	0	0	0	1.0	2.0	0	4.0	0	0	–	10.6	127.4
Biphasic, 70% amplitude	0	0	1.0	0	0	0	1.0	2.0	0	12.0	0	0	–	13.3	95.3
20% CV	0	0	1.0	0	0	0	2.0	2.0	0	6.0	0	0	–	12.3	112.9
20% CV, 70% amplitude	0	0	1.0	0	0	0	2.0	2.0	0	5.0	0.1	0	–	9.9	116.5
50% PW	0	0	1.0	0	0	0	0	2.0	1.0	5.0	0	0	–	10.6	116.6
50% PW, 150% amplitude	0	0	1.0	0	0	0	3.0	2.0	0	8.0	0.1	0	–	12.6	107.3
ET2 (R ViM, 1^{-} C^{+}, 1.5 V, 90 μs, 190 Hz)															
Clinical DBS	0	0	1.5	0	0	0.5	3.5	0	1.0	7.5	0	0	20.4	95.8	88.3
DBS OFF	0	1.0	1.5	0	0.5	1.0	3.0	0	1.0	10.0	0	0	21.8	89.8	83.8
Clinical DBS, 70% amplitude	0	0	1.0	0	0	1.0	3.0	0	1.0	5.0	0	0	19.3	74.1	90.1
Biphasic	0	0	1.0	0	0	1.0	4.0	0	1.0	7.0	0	0	21.9	72.5	90.6
Biphasic, 70% amplitude	0	0	1.0	0	0	1.0	4.0	0	1.0	6.0	0	0	19.8	98.4	85.6
20% CV	0	1.0	1.0	0	0	1.0	2.0	0	1.0	5.0	0	0	21.2	95.1	94.2
20% CV, 70% amplitude	0	1.0	1.0	0	0	1.0	4.0	0	1.0	7.0	0.1	0	21.3	69.3	83.8
50% PW	0	1.0	2.0	0	0	1.0	4.0	0	1.0	9.0	0	0	21.0	96.6	86.5
50% PW, 150% amplitude	0	1.0	1.0	0	0	1.0	4.0	0	1.0	7.0	0	0	19.9	79.1	89.8
ET3 (L ViM, 2^{-} C^{+}, 2.0 V, 90 μs, 130 Hz)															
Clinical DBS	0	0	0	0	0	0	0	0	0	2.5	0	0	8.7	33.6	119.4
DBS OFF	0	0	1.0	0	0	0	0	0	0.5	5.5	0	0	10.5	38.5	116.8
Clinical DBS, 70% amplitude	0	0	0	0	0	0	0	0	0	5.0	0	0	10.0	26.5	120.8
Biphasic	0	0	0	0	0	0	0	0	0	3.0	0	0	10.2	32.9	–

Table 2. *Continued*

	TRS scores								Kinesia scores		PEG test	TUG test	Gait rite
Subject	UE rest tremor	UE postural tremor	UE action tremor	LE rest tremor	LE postural tremor	UE action tremor	Drawing A + B + C	Writing	Pouring	Total score	UE rest tremor	UE postural tremor	Time (s)	Time (s)	Time (s)
Biphasic, 70% amplitude	0	0	0	0	0	0	0	0	0	4.0	0	0	9.8	26.7	116.0
20% CV	0	0	0	0	0	0	0	0	1.0	5.0	0	0	11.5	35.4	98.5
20% CV, 70% amplitude	0	0	0	0	0	0	0	0	0	2.0	0	0	11.1	33.1	123.2
50% PW	0	0	0	0	0	0	0	0	0	4.0	0	0	10.7	27.1	117.3
50% PW, 150% amplitude	0	0	0	0	0	0	0	0	0	2.0	0	0	10.1	28.2	112.5

UPDRS-III sub scores, TRS sub scores and Kinesia scores correspond to the limbs contralateral to the DBS brain target. All UPDRS-III and TRS scores are expressed as medians calculated from assessments by the three neurologists, except for subject PD1, which was assessed by only the two on-site neurologists. The median UPDRS scores from clinical DBS and DBS OFF were also calculated from the assessments at the beginning and end of testing. Values are missing from when DBS settings were not tested or from when assessments were not administered because of subject dropout, equipment malfunction, or lack of equipment availability.

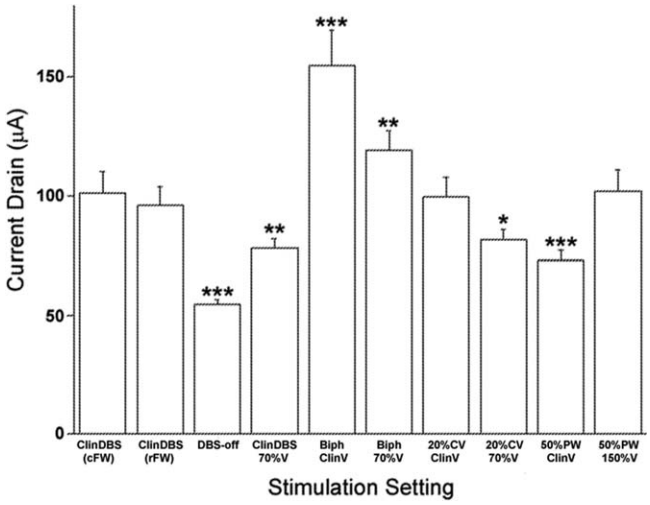

Figure 3. The estimated amount of battery drain associated with each DBS setting. Data are expressed as the average ± SEM current drain across all 11 PD and ET subjects participating in the study for the entire series of settings tested, including the clinically-optimal DBS settings (*ClinDBS*) delivered using the commercial IPG FW (cFW) and also with the research FW (rFW). Data were analyzed using a paired Students *t* test, comparing the current drain with clinically-optimal DBS settings delivered using the cFW to the current drain with each nonconventional setting. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

associated with delivery of the *20%CVClinV* setting (99.83 ± 7.97 μA; $p = 0.69$). In contrast, delivering *BiphClinV* or the *BiphClin70%V* setting was associated with significant increases in current drain (154.75 ± 15.01 μA and 119.35 ± 26.45 μA; $p = 0.17$, $p < 0.0001$, and $p < 0.01$). Therefore, there were no disadvantages in IPG efficiency associated with delivery of the nonconventional DBS settings *per se*, only predictable variations in current drain based on the energy demand of the specific stimulation settings.

DISCUSSION

There is a critical need for novel approaches to optimize the efficacy and efficiency of DBS therapies. While an increasing number of patients benefit from DBS, the improvement for a subset may be limited or offset by side effects. Patients who do benefit from DBS often undergo repeat surgeries to replace IPG batteries, at a rate that depends on the stimulation parameters, electrode configuration, and IPG battery type. Thus, improving the efficacy and efficiency of commercially-available IPGs would likely benefit many patients with DBS.

Although several computational and animal model studies have investigated nonconventional DBS parameters, clinical evaluations have been somewhat limited. In this exploratory study, we tested several nonconventional stimulation settings using a custom DBS-device FW application in PD and ET subjects chronically-implanted with DBS using randomization and blinding. Whereas the primary objective was to assess the feasibility of testing tolerability, assessing the feasibility of testing for efficacy and efficiency were secondary objectives. We found that all of the nonconventional stimulation settings were safe in all subjects and generally well-tolerated. Importantly, we also found that a simple FW upgrade to a commercial IPG may provide more DBS programming options without unexpected disadvantages related to the operating efficiency of the device. Moreover, we also provide preliminary evidence that

Table 3. Subjects' subjective reports of positive and negative perceptions for each of the nonconventional DBS setting tested.

DBS setting	Subjective patient comments (positive and negative)
ClinDBS	PD1: felt transient current surge
DBS-off	PD1: felt tipping over, drunk, shaky, wobbly
	PD2: felt slower, stiffer, and that they could not speak (mute)
	PD5: felt transient hand tingling
	PD6: felt more tremor, stiffness, slowness but that gait was better
	ET1: felt off-balance and that handwriting was poor
BiphClinV	PD1: felt transient current surge
	PD6:felt lip pulling, experienced difficulty speaking*
	PD7: felt ipsilateral tremor was better
	PD8: felt transient strong jolt
	ET1: felt mild jolt in hand
	ET2: felt less secure and that movements were more taxing
	ET3: felt transient hand tingling
Biph70%ClinV	PD1: felt transient current surge
	PD6: felt less tremor, looser, less coordinated hand, but faster gait
	ET1: felt transient tremor in entire body
20%CVClinV	PD1: felt transient current surge
	PD5: felt transient arm tingling
	PD6: felt flashing in the eyes, facial pulling*
	PD7: felt no tremor at all (bilateral)
	PD8: felt strong jolt, dizzy, blurry vision*
	ET1: felt this was a good setting
	ET2: felt more relaxed
	ET3: felt transient tingling but that setting was too strong
20%CV70%V	PD1: felt transient current surge
	PD2: experienced speech difficulty, felt neck stiffness
	PD6: felt better coordinated
	PD7: felt ipsilateral tremor was better
	ET3: felt that movements were slower
50%PWClinV	PD1: felt transient current surge
	PD5: felt transient tingling of both hands
	PD6: felt feel slower and stiffer
	PD8: felt mild transient jolt
50%PW150%V	PD1: felt transient current surge
	PD2: felt transient tingling and that speech was much better
	PD5: felt transient arm tingling
	PD6: felt gait was much better
	PD7: felt no tremor at all (bilateral)
	PD8: felt transient moderate jolt
	ET1: felt transient jolt in finger tips
	ET3: felt transient hand tingling
70%ClinV	PD1: felt a little stiff
	PD2: felt neck was stiffer, speech worse, off-balance
	PD6: experienced flashes in both eyes*
	PD8: felt transient mild jolt
	ET3: felt dexterity was improved

*Intolerable side effects.

charge-balanced biphasic pulses with a square-wave active recharge may offer therapeutic efficacy advantages. Yet, while standard clinical rating scales were useful for detecting different responses to the different stimulation settings, objective assessments of tremor and gait were not, likely due in part to the phenotypic variability across patients (e.g., tremor-dominant vs. akinetic-rigid vs. postural instability with gait dysfunction subtype). Nonetheless, the overall results of this study demonstrate critical feasibility of testing these and other nonconventional DBS therapy concepts in a well-controlled manner.

The results of this study can also be used to guide the design of future studies evaluating nonconventional DBS settings. To obtain the most generalizable results, we tested subjects in the environment where their DBS adjustments and clinical testing were typically performed. This procedure allowed us to enroll subjects who had already been optimized postsurgically. We chose not to study subjects immediately postoperatively to minimize confounding by the micro-lesion effect, and to provide a valid comparison of nonconventional settings vs. clinically optimized settings. The cutoff of four monthly programming sessions used to define clinical optimization was a potential limitation of the current study, although in our experience optimization is often achieved within three to four months after surgery. Although the wash-in plus wash-out period between different stimulation settings may be considered suboptimal, this allowed for screening multiple settings in one session and has been utilized previously (24,26,29,36,45). The 2 min wash-in interval limits our ability to draw firm conclusions about the long-term effects of these nonconventional settings. While acute studies of this nature are ideal for screening multiple nonconventional DBS setting concepts, future statistically powered studies will ideally focus on one specific concept and test in a larger sample over a longer time period.

Stimulation at high frequency (>100 Hz) is typically required to produce motor improvement in PD, and lower frequencies have often been shown to be ineffective (4,9,46). Dorval et al. found evidence suggesting that DBS settings that improve PD bradykinesia during the battery-replacement surgery may do so by entraining basal ganglia activity (26). Compared to continuous DBS delivered at regular frequencies, irregular DBS patterns with same average frequency (10, 20, or 30% CV) did not entrain neuronal activity nor alleviate bradykinesia as effectively, suggesting that regular patterns of DBS are superior. Conversely, Brock et al. (25) tested specific irregular DBS patterns in a similar clinical setting and found that some irregular patterns may in fact deliver greater improvement to PD bradykinesia symptoms. In the current study, we tested irregular DBS patterns with a 20% CV (*20%CVClinV*) in PD and ET patients in a standard clinical environment. In most subjects, the *20%CVClinV* and *20%CV70%V* settings appeared to deliver some benefit compared to the *DBS-off* condition (sham control). In some cases, these irregular DBS pattern settings were even more effective. However, in other cases the irregular DBS patterns were not well-tolerated, as in subject *PD8* who described a persistent "jolt" sensation. Yet, these results demonstrate that it was feasible to distinguish clinical outcomes associated with different patterns of DBS delivered in chronically-implanted subjects in a standard clinical environment.

There is building evidence that narrower pulse widths than commonly used may be associated with wider therapeutic windows. Moro et al. (4) evaluated the effects of >20 DBS settings by varying pulse width, amplitude, and frequency and found that the combination of the highest tolerable voltage with the shortest pulse width was the most effective strategy at treating PD motor symptoms. Results from a more recent open-label study by Reich et al. using a combination of human subject and computational modeling outcomes, suggests that narrower pulse widths may lead to a widening of the therapeutic window through a proportional more efficient activation of neural elements (22). In the current blinded study, we used a 50% narrower pulse width with a proportional 50% increase in amplitude (*50%PW150%V*), and found in some cases that this

setting was generally both at least as effective and efficient as the clinical settings. The narrower pulse width tested at the clinically-optimal amplitude (*50%PWClinV*) was not as effective as the clinical settings and was less tolerable, but drained significantly less battery. Regardless, these results also demonstrate the feasibility of studying the potential therapeutic window benefits of shorter pulse widths using a blinded, randomized study design.

The traditional DBS pulse is composed of a rectangular, active phase and an exponential passive recharge phase, designed to produce an appropriate neural response, a coincident behavioral response, and balance the cathodic phase to prevent tissue damage (30). While investigating the effects of modified pulse shapes on neural activity, Hofmann et al. demonstrated that introducing a short gap between the initial cathodic phase and the anodic phase could result in more effective and more efficient neural entrainment (31). Foutz and McIntyre also evaluated nontraditional pulse shapes, including Gaussian, exponential, triangular, and sinusoidal pulse, finding that some novel pulse shapes may deliver the same neural effects with significantly reduced energy requirements (30). In the current study we tested a nonconventional square-wave biphasic pulse with active cathodic and anodic phases at the subjects' clinically-optimal voltage (*BiphClinV*). The *BiphClinV* setting was well tolerated by nearly all subjects and when delivered at the clinically-optimal voltage appeared even more effective than the clinically-optimal settings. However, the *BiphClinV* setting was obviously associated with a higher energy demand, requiring approximately 50% greater current drain from the IPG battery than traditional DBS biphasic pulses with a passive recharge. At 70% of the clinically-optimal voltage, the square-wave biphasic pulse (*BiphClin70%V*) was both less effective and less efficient than the clinically-optimal settings. Nevertheless, the nonconventional square-wave biphasic pulse may have potential clinical utility to provide symptom-specific relief in select patients who do not respond maximally to the commercially-available settings, especially in those implanted with rechargeable IPG batteries. The potential benefits suggested here deserve further exploration.

In summary, there is a clear need to develop more effective and efficient stimulation paradigms. This study demonstrates the feasibility of evaluating nonconventional DBS patterns in a standard clinical environment using controls, blinding, and randomization. Whether nonconventional settings can be used to alleviate specific side effects of clinical DBS or address specific unaddressed symptoms was not addressed but also requires further study. Furthermore, the potential for simple FW updates to already implanted DBS devices as a means to improve symptom control is a very innovative and appealing approach for optimizing the therapy. The idea of narrower and biphasic pulses will need to be tested in larger clinical trials.

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Authorship Statements

Drs. Akbar, Hack, Okun, Martinez-Ramirez, Skinner, Hess, and DeJesus designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. Akbar prepared the manuscript draft with important intellectual input from Drs. Raike, Okun, Hess, Hack, DeJesus, Martinez-Ramirez, and Skinner. Dr. Raike participated in reviewing data collection, and participated in data analysis. All authors approved the final manuscript. We received no funding for the study. Statistical support in analyzing the data with input from authors Drs. Akbar, Raike, Hack, Okun, Hess, and Skinner. Drs. Akbar, Raike, and Okun had complete access to the study data. We would like to thank Medtronic Inc. for providing the research firmware, equipment, and technical support.

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COMMENTS

The manuscript is well-written and attempts to explore some ideas in treating PD and tremor using DBS by comparing parameter, waveform shape, and timing alterations with typical signals that are used. Although the number of subjects is low and findings studied across measurements would require more power to gain statistical credibility, and the 2-3 hours of single-session study is probably not giving the whole story on whether a particular stimulus pattern would truly be more or less useful in a longer term setting, the study does a reasonable job of trying to explore some of these questions. Interestingly, very few of the changes they tried resulted in better or more efficient stimulation. They note that smaller pulse widths and possibly a rectangular biphasic waveform might be worth studying further, but of course there are other nuances and patterns to be explored additionally not examined in their work. As the field progresses, we are learning more and more that, with most stimuli, the devil is in the details in terms of axon diameter, activating function shape, anodal and cathodal pulse timing, extent, and order, and electrode size and material, not to mention local electrode-tissue interface effects and so forth. The authors can only examine a limited slice of the parameter universe and should not be faulted in that sense. Otherwise, some new clarifications are noted here, even if a little underwhelming.

Jeff Arle, MD, PhD
Boston, MA, USA

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The authors present a well designed experimental protocol that investigates the feasibility of studying various stimulations patterns and shapes in DBS therapy amongst 8PD and 3ET cases. This is an interesting investigation as it calls into question the current standard DBS waveforms and parameters, and prompts further consideration of non-conventional stimulation paradigms that may offer advantages in either symptom control or energy consumption. Investigations such as these have the potential to transform DBS therapy as we currently know it.

Joohi Jimenez-Shahed, MD
Houston, TX, USA

Comments not included in the Early View version of this paper.

