Deep brain stimulation amplitude alters posture shift velocity in Parkinson's disease

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Abstract Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is now widely used to alleviate symptoms of Parkinson's disease (PD). The specific aim of this study was to identify posture control measures that may be used to improve selection of DBS parameters in the clinic and this was carried out by changing the DBS stimulation amplitude. A dynamic posture shift paradigm was used to assess posture control in 4 PD STN-DBS subjects. Each subject was tested at 4 stimulation amplitude settings. Movements of the center of pressure and the position of the pelvis were monitored and several quantitative indices were calculated. The presence of any statistically significant changes in several normalized indices due to reduced/no stimulation was tested using the one-sample *t* test. The peak velocity and the average movement velocity during the initial and mid phases of movement towards the target posture were substantially reduced. These results may be explained in terms of increased akinesia and bradykinesia due to altered stimulation conditions. Thus, the dynamic posture shift paradigm may be an

effective tool to quantitatively characterize the effects of DBS on posture control and should be further investigated as a tool for selection of DBS parameters in the clinic.

Keywords Parkinson's disease · Deep brain stimulation · Posture control · Dynamic posture shifts · Movement velocity

Abbreviations

AR	Akinetic-rigidity
C	Center
CD	Clinically-determined
CD _L	Clinically-determined setting on the day low amplitude was tested
CD _M	Clinically-determined setting on the day moderate amplitude was tested
CD _O	Clinically-determined setting on the day off stimulation was tested
COP	Center of pressure
DBS	Deep brain stimulation
E	East
<i>E_H</i>	Error during holding phase
FOG	Freezing of gait
H&Y	Hoehn & Yahr
Hz	Hertz
LOS	Limits of stability
LOW	Low
MOD	Moderate
MX	Mixed symptoms
N	North
NE	North East
NW	North West
OFF	Off
PD	Parkinson's disease
PL ₁	Pathlength of initiation phase

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PL_M	Pathlength of movement phase
POP	Position of pelvis
STN	Subthalamic nucleus
T	Tremor
T_I	Time of initiation phase
T_M	Time of movement phase
U_H	Unsteadiness of holding phase
UPDRS	Unified Parkinson's Disease Rating Scale
V_I	Velocity of initiation phase
V_M	Velocity of movement phase
V_P	Peak velocity
W	West

Introduction

The control of posture and movement is mediated by the dynamic interactions amongst brain regions such as motor cortex, cerebellum, and basal ganglia. Parkinson's disease (PD), which is caused by degeneration of one region of the basal ganglia, disrupts the network behavior in a manner that is consistent with changes in neurodynamic patterns observed in models of other networks of interacting brain regions (Samson et al. 2010; Wang 2007). In PD, deep brain stimulation (DBS) of the subthalamic nucleus (STN) attempts to re-establish the balance of the brain region interactions (Benabid et al. 1991; Gross and Lozano 2000).

Of the many motor impairments in PD (tremor, muscular rigidity, bradykinesia, posture and gait instability), postural instability can be the most disabling (Bloem et al. 1998, 2001) due to its impact on independence in daily activities and increased risk of falls (Stack and Ashburn 1999). It is characterized by decreased sway velocity (Horak et al. 1992) and postural adaptability (Lakke et al. 1984, 1985). DBS has been shown to improve posture control as indicated by the posture component of the Unified Parkinson's Disease Rating Scale (UPDRS) (Benabid et al. 2000; Bejjani et al. 2000) and postural sway (Rocchi et al. 2002) measures. The improvements provided by STN-DBS in many instances almost paralleled those observed under levodopa therapy and lead to a synergistic summation of effects (Maurer et al. 2003; Colnat-Coulbois et al. 2005) when combined. It has also been shown that STN-DBS improved balance performance even in the absence of anti-parkinsonian medication (Nilsson et al. 2005).

To-date, most studies of DBS efficacy have compared stimulation on/off conditions and have used only a small set of qualitative clinical outcomes measures. While these limitations were justifiable in terms of time, inconvenience, and safety of the subjects, they may provide a very

restricted view of the effects of DBS. Current DBS technology provides a large range of stimulation options involving multiple anatomical targets, electrode geometry, and thousands of pulse train options (specified by pulse width, frequency, and voltage) (Kuncel and Grill 2004). There can be substantial tradeoffs in stimulation parameters selection for best clinical outcomes given the complex neural circuitry and the multi-factorial nature of the clinical symptoms.

In this study, a dynamic posture shift paradigm with visual biofeedback was utilized to identify postural measures that can be easily obtained in clinics for effective DBS programming. Although all stimulation pulse parameter settings will impact the influence of DBS, we focused on pulse amplitude because it is typically varied by clinicians in an attempt to optimize the effect of the DBS system for the individual and it is considered to be the most critical factor to obtain adequate alteration in STN activity (Moro et al. 2002). Each subject was tested at 4 different stimulation amplitude settings. The assessment was designed to mimic the postural shifts performed during daily activities such as reaching. It has been shown that reaching tasks challenge postural stability in severe PD (Stack et al. 2005) and therefore this paradigm may provide insight into the effects of STN-DBS on postural stability. Our results indicate that the peak velocity and mean velocity during initial and mid phases of the dynamical shifts movements during target reach were affected by changes in DBS stimulation amplitude and these may be useful indices in the clinic to optimize DBS settings for posture control.

Methods

Subjects

Four subjects with implanted DBS of STN participated in this study (average age: 62.2 years; age range: 50–77 years) (Table 1). Each subject exhibited a different primary clinical feature of PD, namely: tremor (T), akinetic-rigidity (AR), freezing of gait (FOG), and mixed symptoms (MX). Each subject signed an informed consent form approved by the Institutional Review Boards at Banner Good Samaritan Medical Center and Arizona State University before participating in the study.

Protocol

Subjects were eligible for this study if they were aged 18–80, had a diagnosis of idiopathic PD with bilateral symptoms, a Hoehn & Yahr (H&Y) score of 4 or less in 'off-stimulation' state, and an implanted DBS system for at

Table 1 Subjects' characteristics, daily medication, and DBS stimulation parameters: The abbreviations AR, MX, FOG and T represent subjects' major symptom such as akinetic rigidity, mixed symptoms, freezing of gait and tremor, respectively

Conditions \ subjects	Subject 1-AR (54, M, 12, 1.5)	Subject 2-MX (77, M, 11, 1)	Subject 3-FOG (68, M, 10, 1)	Subject 4-T (50, F, 12, 3)
CD_M				
Medication (LEDD) (mg)	450	2,225	800	390–650
Frequency (Hz)	185 L	135 R; 135 L	185 R; 185 L	185 R; 185 L
Polarity	1–, C+L	3–, 1+R; 3–, 1+L	1–, C+R; 1–, C+L	1–, 3+R; 1–, 3+L
Pulse width (μs)	90 L	60 R; 60 L	90 R; 90 L	90 R; 90 L
Amplitude (V)	3.7 L	2.5 R; 2.5 L	4.1 R; 3.9 L	5.0 R; 5.0 L
MOD				
Amplitude (V)	2.6 L	1.8 R; 1.8 L	2.9 R; 2.8 L	3.5 R; 3.5 L
CD_L				
Medication (LEDD) (mg)	450	2,450	800	390–650
Frequency (Hz)	170 L	135 R; 135 L	185 R; 185 L	185 R; 185 L
Polarity	1–, C+L	3–, 1+R; 3–, 1+L	1–, C+R; 1–, C+L	1–, 3+R; 1–, 3+L
Pulse width (μs)	90 L	60 R; 60 L	90 R; 90 L	90 R; 90 L
Amplitude (V)	3.6 L	2.5 R; 2.5 L	4.1 R; 3.9 L	5.0 R; 5.0 L
LOW				
Amplitude (V)	1.1 L	0.8 R; 0.8 L	1.3 R; 1.1 L	1.5 R; 1.5 L
CD_O				
Medication (LEDD) (mg)	450	2,450	800	390–650
Frequency	185 L	135 R; 135 L	185 R; 170 L	185 R; 185 L
Polarity	1–, C+L	3–, 1+R; 3–, 1+L	1–, C+R; 1–, C+L	1–, 3+R; 1–, 3+L
Pulse width (μs)	90 L	60 R; 60 L	90 R; 90 L	90 R; 90 L
Amplitude (V)	3.7 L	2.5 R; 2.5 L	3.8 R; 4.1 L	5.0 R; 5.0 L
OFF				
Amplitude (V)	No stim	No stim	No stim	No stim

The numbers within parenthesis indicate age, sex, number of years after diagnosis of PD, and number of years after DBS implantation. CD_M, CD_L and CD_O stands for clinically determined optimum settings on which moderate (MOD), low (LOW) and off (OFF) conditions were performed, respectively. In the MOD and LOW conditions, the amplitude of stimulation was reduced by 30 and 70 %, respectively, from that of during clinically determined stimulation parameters. During the OFF condition, stimulation was completely off. The medication dosage is expressed in terms of levodopa equivalent daily dose (LEDD). The right and left sides are indicated by 'R' and 'L' respectively. All the subjects except subject 1 have DBS units implanted bilaterally. Polarity gives the electrodes chosen for stimulation. If the case of the neurostimulator is chosen as anode (positive electric potential), then it is a unipolar stimulation whereas if two different electrode contact sites (out of four available) are chosen for stimulation, then it is a bipolar stimulation. Only the stimulation amplitude is changed for MOD and LOW altered conditions compared to that of their corresponding CD conditions and all other stimulation parameters were maintained the same. But during the OFF condition, the stimulation is completely switched off indicated as 'No stim'

least 3 months. Exclusion criteria included the presence of: significant hepatic, renal, cardiovascular, endocrinological, or respiratory disorder; Parkinson's plus syndrome, or unstable neurological disease other than PD; history of chronic psychiatric disorder, drug dependence, intellectual impairment, or cerebral insult (causing delayed secondary PD); or a score of 4 or greater for H&Y stage when medicated or for specified elements of the UPDRS. All experimental data collection sessions were conducted at Banner Good Samaritan Medical Center.

Four stimulation conditions were tested: (1) clinically-determined (CD; i.e., specified by the subject's physician), (2) moderate (MOD; ~70 % CD pulse amplitude), (3) low (LOW; ~30 % CD pulse amplitude), and (4) off (OFF; no

stimulation). The percentage values listed are approximate due to the limited resolution of the implanted pulse generator and pulse amplitude never exceeded the CD levels due to the likelihood of eliciting adverse effects. The CD stimulation amplitude setting was used as a base for normalization in order to account for subject-to-subject variations in baseline stimulation levels. Subjects were tested in the morning during 'medication-on' state on three different days, each separated by a time period of 2–4 weeks. The subjects' anti-parkinsonian medication dosages and frequencies were not altered for these experiments. On a given day, data were collected first at the CD setting, and at one of the three altered settings. In the text and figures, the trials with the CD setting have been labeled by the altered

setting that was tested on that day, i.e., CD_M , CD_L , and CD_O refer to the trials at the CD setting on the day that the MOD, LOW, or OFF conditions were tested, respectively. Stimulation levels and responses for each of the three altered stimulation settings were normalized by their corresponding CD values. Table 1 gives the values of stimulation settings used during altered stimulation conditions for each subject.

Each experimental session consisted of a set of postural tests and a clinical evaluation using UPDRS for each of the 2 stimulation settings. Postural tests were first performed at the CD settings followed by evaluation using Part-II (Falling, Freezing, and Walking sections), Part-III (Motor Examination), and Part-V (H&Y staging) of UPDRS. The DBS pulse amplitude was then changed from CD to one of the three altered stimulation conditions. A wait-period of 20 min was imposed to allow the stimulation parameter change to take effect. The postural tests and clinical evaluations were again conducted in the altered stimulation condition followed by changing the stimulation back to the CD setting. The experiment was concluded after a wait-period to ensure that the subjects felt that their symptom severity had returned to the level that was typical for the CD settings.

During the posture control trials, subjects were asked to stand on force platforms, in a hip-width (distance between the anterior superior iliac spines) stance. A lightweight electromagnetic sensor was mounted on the back of the pelvis to measure the position of the pelvis (POP). The center of pressure (COP) was calculated using ground reaction forces obtained from the force platforms sampled at 2.5 kHz and low pass filtered at 2 Hz using a first order digital Butterworth filter. After filtering, the

signal was down-sampled at 25 Hz. The COP reflects body sway to maintain the center of gravity within the support base. Three trials were performed for each of the COP and POP biofeedback paradigms for each stimulation setting. For each trial, subjects viewed a computer monitor placed at eye level which provided biofeedback of postural shifts as movements of a cursor representing either the COP or POP but subjects were blinded to the type of biofeedback displayed. Subjects were asked to move the cursor from the center target (C) to 1 of 5 outer targets (at compass directions W, NW, N, NE, and E) by shifting posture and to hold the cursor within the target as close as possible to the target center for 2 s (Fig. 1). The presentation of each outer target location was followed by presentation of the center target. After the appearance of a target, the subject would shift their posture to move the cursor into the target. When the cursor resided in the target for 2 s, the target was considered acquired and it disappeared. Then the next target would appear in another location. If the target was not acquired within 10 s, the target disappeared and the next target was presented in another location (refer to Fig. 1 for target sequence). The movements from center to outer targets E, N and W (and back) were presented twice and the other targets were presented once per trial for each type of biofeedback under each stimulation setting therefore resulting in 16 target presentations per trial.

The radial distance between the starting point and the outer targets (magnitude of the posture shift) and the size of the targets were set as 30 % and 10 % of limits of stability (LOS), respectively, thus individualized for each person as a percentage of their LOS (Hamman et al. 1992). The movement required to successfully complete the task did

Fig. 1 Subject moves to the target circle from the start point. Position of pelvis (POP) movement of a subject with DBS during movement to and from each target in one trial. During each trial, the same

following sequence of tasks were presented: $C \rightarrow NE \rightarrow C \rightarrow E \rightarrow C \rightarrow N \rightarrow C \rightarrow W \rightarrow C \rightarrow NW \rightarrow C \rightarrow E \rightarrow C \rightarrow N \rightarrow C \rightarrow W \rightarrow C$. LOS stands for limits of stability

not require the subject to lift their feet from the force plate at any time.

Data analysis

The UPDRS and several quantitative indices (described below) derived from the experiments were used to evaluate posture control. All indices were obtained using horizontal plane (mediolateral, anteroposterior) measurements of COP and POP during successful target reach. The time-series for each target path was divided into three segments: initiation phase (starting point up to 10 % LOS distance), mid phase (10 % LOS distance to initial target entrance), and hold phase (movement inside the target from the last target entry until successful completion of target-hold). The following indices were calculated using the data segments.

The indices PL_I (*Path Length*—sum of the Euclidian distances traveled), T_I (*Time taken*—time taken to cover the path length), V_I (*Velocity*—mean of instantaneous velocities) were calculated from the initiation phase. Corresponding indices PL_M , T_M , and V_M were calculated for the mid phase data segment.

Using the hold phase data segment, E_H (*Error*—mean of the distances between the cursor and the center of the target), U_H (*Unsteadiness*—standard deviation of the distances between the cursor and the center of the target), EC (*Entry count*—number of times the subject enters the target circle), were calculated. E_H and U_H quantify accuracy and variability during the hold phase, respectively.

In addition, V_P (*Peak Velocity*), the maximum velocity achieved during any point of time during target reach (includes initiation, mid, and hold phases) was also calculated.

These indices were calculated for each trial during CD and altered setting conditions for each session. The values were averaged across trials to obtain a single value for a given target and index. The degree of change in any index from the CD condition to the altered stimulation condition on a given day was calculated as $X_i = (x_{i,ALT} - x_{i,CD}) / x_{i,CD}$, where x is the index of interest, and i the target number. As 10 different targets were presented during the task, X has the sample size of 10 and it was tested against the value of zero using one sample t test ($p < 0.05$) to determine the statistical significance of the change in any particular index due to altered stimulation condition for each subject. The normalization of various indices obtained during MOD, LOW, and OFF conditions (dividing by the value at corresponding CD condition such as CD_M , CD_L , or CD_O) was performed to facilitate comparison of changes in a particular index across altered stimulation conditions and subjects (Fig. 2). Therefore, the analysis presents only three conditions because each altered condition was normalized by CD condition on that day.

Results

Several quantitative indices were influenced by changes in the stimulation amplitudes both in the COP and POP visual feedback conditions. Of the total number of 24 possibilities for each index (4 subjects, 3 altered settings, 2 feedback conditions), the velocity measures showed statistically significant changes for the most number of cases due to altered stimulation settings. Specifically, the measures V_I , V_M , and V_P were significantly altered for 12, 11, and 12 cases respectively whereas PL_I , T_I , PL_M , T_M , E_H , U_H , and EC were changed significantly only for 8, 10, 1, 7, 4, 2, and 6 cases, respectively. When comparing the different forms of feedback conditions, of the 120 cases (10 indices, 3 altered conditions, 4 subjects) both the COP and the POP feedback produced significant changes in almost same number of cases, 31 and 30 respectively. Furthermore, in both feedback conditions, the LOW setting resulted in a larger number of significant changes (13 cases each in COP and POP feedback conditions) than the OFF setting (COP: 8; POP: 11 cases) and the MOD setting (COP: 10; POP: 6 cases). Across the subjects, the one with tremor as a major symptom was most affected by alterations in stimulation showing significant changes (COP: 10; POP: 13 cases). The subject with the major symptom of FOG showed changes in 9 cases each in COP and POP; the subject with AR showed changes in 8 cases in COP and 4 cases in POP, and the subject with MX showed changes in 4 cases each in COP and POP. The normalized changes in V_I and V_M for COP feedback are shown in Fig. 2.

Since velocity measures were more consistently affected, the influence of path length and time on those measures was also explored (Fig. 3). Of the total number of 120 cases per feedback condition (4 subjects, 10 targets, 3 altered conditions), during the initiation phase, irrespective of statistical significance, a decrease in V_I was observed for 83 % (COP feedback) and 73 % (POP feedback) of cases. Reduction in V_I was often coincident with a decrease in PL_I (COP: 86 %; POP: 64 % of cases) and/or coincident with an increase in T_I (COP: 61 %; POP: 77 % of cases). During the mid phase, irrespective statistical significance, a decrease in V_M was observed for 72 % (COP feedback) and 80 % (POP feedback) of cases and this was coincident with decrease in PL_M (COP: 48 %; POP: 42 % of cases) and/or coincident with an increase in T_M (COP: 77 %; POP: 77 % of cases). With COP feedback, the LOW setting exhibited the highest number of instances of reduced velocity followed by OFF and MOD settings, respectively.

Discussion

In this study we have established a visual biofeedback paradigm involving dynamical balance shift tasks to obtain

Fig. 2 Notched box plot comparing changes in normalized (with respect to the value at CD condition on a given day) velocity measures (in %) namely V_I (velocity during initiation phase), V_M (velocity during mid phase), and V_P (peak velocity during entire trial) for four different subjects and data pooled from all the subjects for COP and POP feedback conditions. The MOD, LOW, and OFF conditions are represented by circles, squares, and triangles, respectively and the mean values are represented by black squares. Values

less than zero indicate that the corresponding measure has decreased due to altered stimulation condition and vice versa. The box (lower end) starts at 1st quartile and ends at 3rd quartile. ‘—’ represents minimum and maximum values, ‘x’ represents 1st and 99th percentiles, and ‘—’ attached to the box indicates 5th and 95th percentiles. The subjects and conditions that showed statistically significant reduction ($p < 0.05$ using one-sample t test) in V_I , V_M , and V_P were indicated by ‘*’.

a unique characterization of the effects of STN-DBS on postural control. The posture shifts were designed to activate postural control mechanisms that one uses during daily tasks such as reaching while standing. The task enables quantitative and objective characterization of posture control and can be useful to quantify the effects of DBS in the clinic.

This study identified that velocity measures (V_I , V_M , and V_P) were consistently affected when the stimulation amplitude was reduced and during no stimulation condition. The changes observed in these measures are likely to be related to effects of DBS on different symptoms of PD. For example, the decrease in V_I was mostly due to decrease in PL_I (Fig. 3) and may be attributed to intensified akinesia

(Guehl et al. 2006) and may be similar to the reductions in upper limb reaction time (Kumru et al. 2003; Vrancken et al. 2005) observed during reduced stimulation conditions. This may also be due to increased rigidity during altered conditions (Bejjani et al. 2000; Bartolic et al. 2005) that were observed in the neck, upper and lower extremities, especially in subjects with FOG and tremor as evaluated by UPDRS-part III. The intensified akinesia might have led to increase in T_I observed for some cases. The reductions in V_M and V_P that were mostly due to increases in T_M (Fig. 3) may be due to increased bradykinesia, decreased ankle strength, and abnormal electromyographic patterns during altered stimulation conditions. That is, the reduction in stimulation amplitude decreased movement velocity and this reversed the positive effects of clinically selected stimulation amplitude on these symptoms that have been documented previously (Vaillancourt et al. 2004, 2006). This slowness of the movement might have led to a more direct movement, therefore resulting in the observed reduction in PL_M . In most instances, the velocity measures were affected more by LOW setting than the OFF setting suggesting that some stimulation is not necessarily better than no stimulation thus stressing the importance of

selecting optimum stimulation parameters. The possibility of dyskinesias affecting these measures was also minimal as no subjects were noticeably dyskinetic. These preliminary results indicate that deterioration of particular PD symptoms impairs postural stability.

Two key factors that could have influenced the results were the medication state and the duration of the wait-period after changing the DBS settings. In this study, we chose to test all subjects in their regular medication ‘on’ state. Although several studies have defined the medication ‘on’ state as suprathreshold dosage of levodopa (Guehl et al. 2006), here, the medication ‘on’ state represents their daily living condition and therefore it is the most clinically relevant situation. More importantly, if these measures are eventually utilized in the clinic, it would be preferable to explore different stimulation conditions in the medication ‘on’ state. Also, after DBS amplitude reduction, a resting time period of 20 min was allowed for the change to take effect. Although there may be effects that occur over a longer time period (of hours or days) (Temperli et al. 2003), prior studies (Moro et al. 2002; Kuncel et al. 2006) have suggested that this time period is sufficient to unmask the primary effects of the new settings and to accommodate any transients. This assumption was supported by subjective reports from the subjects that they felt ‘back to normal’ within 10–20 min after restoring the stimulation to the CD settings.

This study has focused on the effects of varying stimulation amplitude on postural control because it is the most critical factor to induce adequate alteration in STN activity (Moro et al. 2002). Our results are at least qualitatively consistent with the basic hypothesis that increasing stimulation amplitude produces changes in motor behavior by progressively recruiting more neural tissue in the vicinity of the electrode that modulates the given behavior. The observation that the altered stimulation conditions are similar to each other but different from the CD setting suggests that the CD amplitude may have a threshold effect on posture. That is, the effect on posture is minimal until stimulation exceeds a threshold that activates specific neural structures.

Parkinsonian tremor, which is a common symptom that can be altered by DBS, is generally observed in the frequency range of 3–6 Hz. To determine if tremor may have affected our results, we calculated the power spectral density of COP and POP data (details not provided due to the length limitations). Across the set of trials at different stimulation levels, results indicated dominant power at about 1 Hz with very little power at frequencies greater than 1 Hz. These indicate that even if tremor existed, the effects were not transferred to COP and POP data, possibly due to inertial properties of the large body mass and the stabilizing effect of having both the feet on the ground.

Fig. 3 Distribution of categories of velocity reduction. The trials in which a velocity reduction was observed were categorized based on the direction of change in PL and T from the CD to the altered setting. For example, if path length decreased and T increased from the CD to altered setting, it was categorized as ‘(-, +)’. The stacked column bar chart represents the distribution of the trials across these categories for the initiation and mid phases for COP and POP feedback conditions. Note that there were no trials that fell into the (+, -) category. Data points from all the different altered stimulation conditions (MOD, LOW, and OFF) and subjects are included. These plots demonstrate that in the initiation phase, reduced velocity was most often associated with a more direct path (reduced path length) and that during the mid phase, reduced velocity was most often associated with increased time

Since only 4 subjects were included in this initial study, we analyzed each subject individually and pooled the data from all the target directions to detect statistically significant changes in the measures cited. The ability to analyze each subject individually was facilitated by the protocol design, which gathered an extensive data set from each individual under various conditions enabling an extensive and detailed characterization of the effects of changing stimulation on quantitative measures of posture control.

With only one measure from the UPDRS from each setting, we were unable to statistically analyze the UPDRS data from each subject individually. Therefore, we pooled the UPDRS data across subjects, but with this sample size, we did not detect consistent changes in the UPDRS scores. This may be due to the low sensitivity of the UPDRS or inconsistency across the subject pool.

This study is one of the few studies in the literature that have presented results across several days in multiple conditions and this data set provides a valuable contribution to the literature. Even with limited number of subjects, the results of this study indicate that these measures, which can be efficiently obtained in the clinic, may enable rapid assessment and iterative optimization of DBS settings for posture control. In addition, these measures may also be used to verify that a setting selected to improve any other particular symptom of PD does not have an adverse effect on posture control.

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References

- Bartolic A, Pirtosek Z, Rozman J et al (2005) Postural stability of Parkinson's disease patients is improved by decreasing rigidity. *Eur J Neurol* 12(2):156–159
- Bejjani BP, Gervais D, Arnulf I et al (2000) Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 68(5):595–600
- Benabid AL, Pollak P, Gervason C et al (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 337(8738):403–406
- Benabid AL, Koudsie A, Benazzouz A et al (2000) Subthalamic stimulation for Parkinson's disease. *Arch Med Res* 31(3):282–289
- Bloem BR, Beckley DJ, van Hilten BJ et al (1998) Clinimetrics of postural instability in Parkinson's disease. *J Neurol* 245(10):669–673
- Bloem BR, van Vugt JP, Beckley DJ (2001) Postural instability and falls in Parkinson's disease. *Adv Neurol* 87:209–223
- Colnat-Coulbois S, Gauchard GC, Maillard L et al (2005) Bilateral subthalamic nucleus stimulation improves balance control in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 76(6):780–787
- Gross RE, Lozano AM (2000) Advances in neurostimulation for movement disorders. *Neurol Res* 22(3):247–258
- Guehl D, Dehail P, de Seze MP et al (2006) Evolution of postural stability after subthalamic nucleus stimulation in Parkinson's disease: a combined clinical and posturometric study. *Exp Brain Res* 170(2):206–215
- Hamman RG, Mekjavic I, Mallinson AI et al (1992) Training effects during repeated therapy sessions of balance training using visual feedback. *Arch Phys Med Rehabil* 73(8):738–744
- Horak FB, Nutt JG, Nashner LM (1992) Postural inflexibility in parkinsonian subjects. *J Neurol Sci* 111(1):46–58
- Kumru H, Summerfield C, Valdeoriola F et al (2003) Effects of subthalamic nucleus stimulation on characteristics of EMG activity underlying reaction time in Parkinson's disease. *Mov Disord* 19(1):94–100
- Kuncel AM, Grill WM (2004) Selection of stimulus parameters for deep brain stimulation. *Clin Neurophysiol* 115(11):2431–2441
- Kuncel AM, Cooper SE, Wolgamuth BR et al (2006) Clinical response to varying the stimulus parameters in deep brain stimulation for essential tremor. *Mov Disord* 21(11):1920–1928
- Lakke JP (1985) Axial apraxia in Parkinson's disease. *J Neurol Sci* 69(1–2):37–46
- Lakke JP, van Weerden TW, Staal-Schreinemachers A (1984) Axial apraxia, a distinct phenomenon. *Clin Neurol Neurosurg* 86(4):291–294
- Maurer C, Mergner T, Xie J et al (2003) Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. *Brain* 126(Pt 5):1146–1163
- Moro E, Esselink RJ, Xie J et al (2002) The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology* 59(5):706–713
- Nilsson MH, Tornqvist AL, Rehnström S (2005) Deep-brain stimulation in the subthalamic nuclei improves balance performance in patients with Parkinson's disease, when tested without anti-parkinsonian medication. *Acta Neurol Scand* 111(5):301–308
- Rocchi L, Chiari L, Horak FB (2002) Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73(3):267–274
- Samson RD, Frank MJ, Fellous JM (2010) Computational models of reinforcement learning: the role of dopamine as a reward signal. *Cogn Neurodyn* 4(2):91–105
- Stack E, Ashburn A (1999) Fall events described by people with Parkinson's disease: implications for clinical interviewing and the research agenda. *Physiother Res Int* 4(3):190–200
- Stack E, Ashburn A, Jupp K (2005) Postural instability during reaching tasks in Parkinson's disease. *Physiother Res Int* 10(3):146–153
- Temperli P, Ghika J, Villemure JG et al (2003) How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology* 60(1):78–81
- Vaillancourt DE, Prodoehl J, Verhagen Metman L et al (2004) Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson's disease. *Brain* 127(Pt 3):491–504
- Vaillancourt DE, Prodoehl J, Sturman MM et al (2006) Effects of deep brain stimulation and medication on strength, bradykinesia, and electromyographic patterns of the ankle joint in Parkinson's disease. *Mov Disord* 21(1):50–58
- Vrancken AM, Allum JH, Peller M et al (2005) Effect of bilateral subthalamic nucleus stimulation on balance and finger control in Parkinson's disease. *J Neurol* 252(12):1487–1494
- Wang L (2007) Interactions between neural networks: a mechanism for tuning chaos and oscillations. *Cogn Neurodyn* 1(2):185–188