

# Long-Term Effects of Thalamic Deep Brain Stimulation on Force Control in a Patient with Parkinson's Disease-Driven Action Tremor

Karen L. Francis, PhD\*

Waneen W. Spirduso, EdD†

Tim Eakin, PhD†

Pamela Z. New, MD‡

*\*Department of Exercise and Sports Science, University of San Francisco, San Francisco, California*

*†Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, Texas*

*‡Department of Neurosurgery, Baylor College of Medicine, Houston, Texas*

**KEY WORDS:** force control, tremor, thalamic deep brain stimulation, Parkinson's disease, coordination, manual dexterity

## ABSTRACT

It is well known that thalamic deep brain stimulation (DBS) in the ventral inter-medius nucleus (VIM) reduces contralateral tremor. However, the ways in which VIM DBS alters force control in patients with Parkinson's disease (PD) are not currently known. The goal of this project was to characterize the effect of VIM DBS on force control of a tremor-dominant Parkinson's patient.

The patient was evaluated before, and at 3, 6, and 13 months after surgery. The study task required independent,

controlled application and release of force by the thumb and index finger to trace a template.

Thalamic stimulation resulted in tremor reduction and improvement in force control of the contralateral (preferred) hand. However, differences in force control remained. When compared to a control subjects' preferred hand and to the ipsilateral (non-preferred) hand, the contralateral hand had a lower concordance phase value. This demonstrates a greater tendency for the changes in force trajectories to be in different directions in contrast to the same direction as is required to perform the task.

In this PD patient, thalamic stimulation resulted in improvement in force control, although the control remains different than that exhibited by a control subject with no known neuropathology.

## INTRODUCTION

It is well documented that Parkinson's disease (PD) impairs the ability to control and coordinate forces between the digits.<sup>1</sup> Tremor that persists during movement may be a contributing factor to the observed impairment in manual dexterity; even though it is resting tremor, not action or postural tremor, that is typically associated with PD. Resting tremor can be a socially devastating motor symptom even though this type of tremor has minimal impact on the ability to perform activities of daily living.<sup>2</sup> Tremor that persists during movement can be functionally devastating and, if not managed, may lead to a loss of independence.

Several researchers have found that action tremor is present in patients with PD.<sup>1,3</sup> It has been shown that patients with tremor-predominant PD have impairments in force control and coordination that are present even after examining this component of aggregate force output data following the separation of tremor by a decoupling method.<sup>1,4</sup> Those data suggest that PD may be associated with losses in finger dexterity and that such losses may be exacerbated by action tremor.

Initially individuals diagnosed with PD are treated with antiparkinsonian medication. However, individuals who become refractory to medication may be candidates for other treatment options. High frequency deep brain stimulation (DBS) is an accepted treatment for patients with PD and other movement disorders.<sup>2</sup> Results from several studies have consistently demonstrated that DBS of the ventral intermediate nucleus of the thalamus (VIM) leads to a reduction in tremor contralateral to the implantation site.<sup>5,6</sup> Results from one of the few long-term studies demonstrated that stimulation was associated with stable tremor control and an improvement

in activities of daily living. However, the majority of these studies are short term and there is a limited knowledge base regarding the long-term efficacy of thalamic stimulation.

Less is known about the effect that high frequency stimulation has on changes in force control and coordination and no known study has examined the effect of thalamic stimulation on force control and coordination in a longitudinal design. A cross-sectional study of DBS of the subthalamic nucleus and the internal segment of the globus pallidus on force control and coordination revealed that stimulation led to increases in maximum pinch force production and improvements in force control parameters in a bimanual task.<sup>7</sup> Increases in maximum force production were greater contralateral to the implantation site, however increases were also noted on the ipsilateral side. It has been well established that implantation of VIM DBS leads to a reduction in the level of confounding tremor,<sup>5,6</sup> however the extent to which VIM DBS leads to more efficient finger dexterity is less clear.

The purpose of this case study was to characterize the effects of VIM DBS in a person diagnosed with PD who was tremor predominant and experiencing both resting and action tremor, on the contralateral and ipsilateral control of force. Specifically, we explored the following questions: (1) Does VIM DBS reduce tremor and improve force control? (2) Is the reduction and improvement in force control and coordination stable across time? (3) Is tremor reduced and is force control more accurate on the contralateral and ipsilateral side of the device implantation after VIM DBS? (4) Do the contralateral (preferred) and ipsilateral (non preferred) hand differ in force control prior to and following stimulation?

## **METHODS**

### **Patient and Control Subject**

A 45-year-old right-handed woman was diagnosed with idiopathic Parkinson's disease. Tremor had been present in the right hand for approximately 3 years. The tremor had increased in magnitude throughout that time period and had resulted in complete functional impairment of the right hand by the time our force control and tremor studies commenced. The tremor was not responsive to medication. DBS implantation was offered to the patient as a treatment option. Prior to implantation the patient signed an informed consent affirming her willingness to participate in the study. The patient passed screening tests for vision, manual digit strength, and medical stability. The patient was measured 2 weeks prior to DBS implantation and 3, 6, and 13 months following DBS implantation. The DBS device was implanted into the left VIM nucleus of the thalamus. Testing for this participant was scheduled for 1-hour post-medication and the medication regimen remained the same post-operatively as pre-operatively.

A 44-year-old right-handed woman who had no known neuropathology served as the control subject. This subject completed the same questionnaires, screening criteria, and informed consent as the patient.

### **Instrumentation**

The Manual Force Quantification System (MFQS) apparatus (The University of Texas: Aging Motor Behavior Laboratory, Austin, TX) and the mathematical basis for the decoupling methodology used to separate components of tremor and aggregate force control data are described in detail in previous papers.<sup>1,4</sup> The MFQS was used to collect 100 Hz time series of aggregate isometric force impulse mag-

nitudes. Data were collected from independent strain gauge transducers mounted 180° with respect to each other as the participant simultaneously applied or released pressure with the thumb and index finger of the same hand on each of the two transducer surfaces. The console was interfaced with a computer screen displaying a cursor whose horizontal position was linearly related to force applied by the thumb and whose vertical position was linearly related to force applied by the index finger. A tracing line template represented points of equal force from both digits in the range from 0.98 to 4.45 N. At each end of the tracing line was a target circle with a 0.098 N radius of acceptance. Specification of sampling rate, radius of acceptance for the target circle, and location of the tracing line are parameters that can be changed on the control screen. All instrumentation settings and data acquisition procedures were controlled through a National Instruments DAQ board using LabVIEW (National Instruments, Austin, TX).

### **Procedure**

At each testing session, the patient performed the task in two blocks of five trials with each hand. The blocks were alternated between hands, starting with the least affected side (left). The control subject was tested using the same protocol on a single occasion.

The goal of the task was to trace the template line by increasing force from both digits at the same rate between two target circles and then to retrace it back to its origin by a controlled decrease of force from both digits at the same rate. Emphasis was on accuracy, keeping the cursor as close to the template line as possible, but the participant was also instructed to try finishing the task as quickly as possible while maintaining accuracy and control.

## Measures

The following components were selected to represent the voluntary control of force and tremor by each digit:

*Root mean square error (RMSE)* - the root mean square of the perpendicular displacements of the cursor from the tracing line while performing the task;

*Force magnitude difference (FMD)* - the magnitude of difference in force produced by the thumb and index finger;

*Temporal performance* - the time taken, with resolution in hundredths of seconds, to traverse the template;

*Concordance phase* - the fraction of time that the trajectories of force impulses from the two digits are changing in the opposite direction with respect to the laboratory frame of reference, scaled by a factor of 180. If the changes in trajectories are always in the same direction, the concordance phase is 180 and conversely if the changes in trajectories are never in the same direction, the concordance phase is 0; and

*Frequency difference* - the frequency at maximum power for the finger subtracted from the frequency at maximum power for the thumb within the 5-7 Hz range during a particular trial.

Each of these measure was calculated for the right (preferred) and left (non-preferred) hand for the patient and control subject.

## RESULTS

Prior to thalamic stimulation, this patient could not perform daily activities that required precise control of the digits of her right hand. Thalamic stimulation resulted in tremor reduction and improvement in force control ability of the contralateral hand. The changes observed at 3 months post-DBS remained stable across a period of 10 months, therefore in the results section we will focus on the differences between the initial measurement pre-DBS and the final measurement post-DBS.

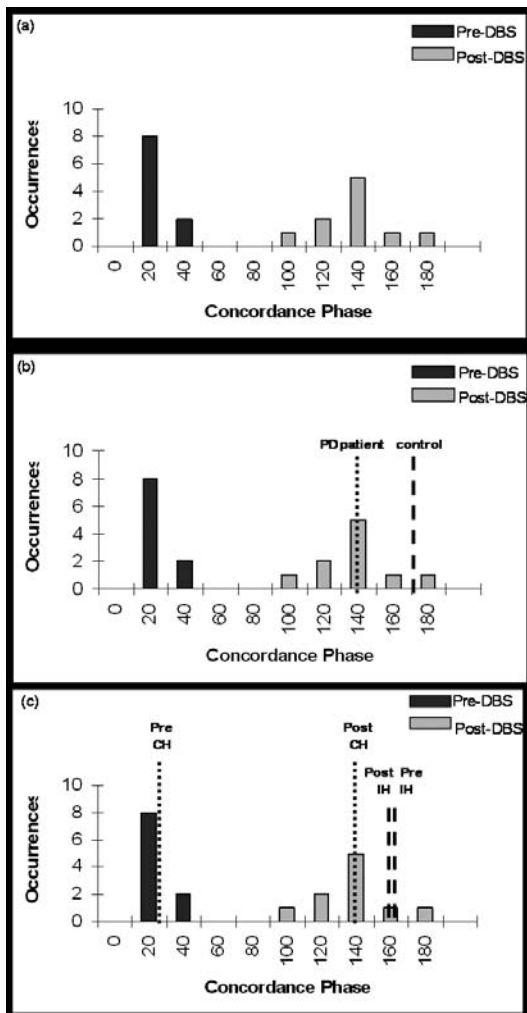
Minimal changes occurred in the ipsilateral hand relative to the device implantation site. Interestingly, performance of the ipsilateral hand 13 months after the surgery continued to be more skillful than that of the contralateral hand. These results suggest that, while DBS implantation clearly improves force control, there are still differences in the force control between the hands that are in the opposite direction of what would be expected between the preferred and non-preferred hand performance.

Results demonstrated that, for the contralateral hand, VIM DBS was associated with improvements in the majority of force control variables and a reduction of the impact of tremor variables. High frequency stimulation resulted in an 88% reduction of RMSE mean values for the contralateral hand. There was improvement of the ipsilateral hand, however the improvement was only 12% of the improvement of the contralateral hand.

The post-DBS variable values for the contralateral hand were similar to the pre-DBS values for the ipsilateral hand.

The FMD mean and standard deviation values of the contralateral hand revealed a similar trend; the mean and standard deviation values were three times greater pre-DBS than post-DBS. There were substantial differences between the contralateral and ipsilateral hand both pre- and post-DBS. As with the RMSE findings, the post-DBS values of the contralateral hand were similar to the pre-DBS values of the ipsilateral hand.

In contrast to changes in accuracy and inter-digit coordination, there were no temporal changes within either the contralateral or ipsilateral hand. However, there was an absolute difference between hands in that the contralateral hand was four times slower

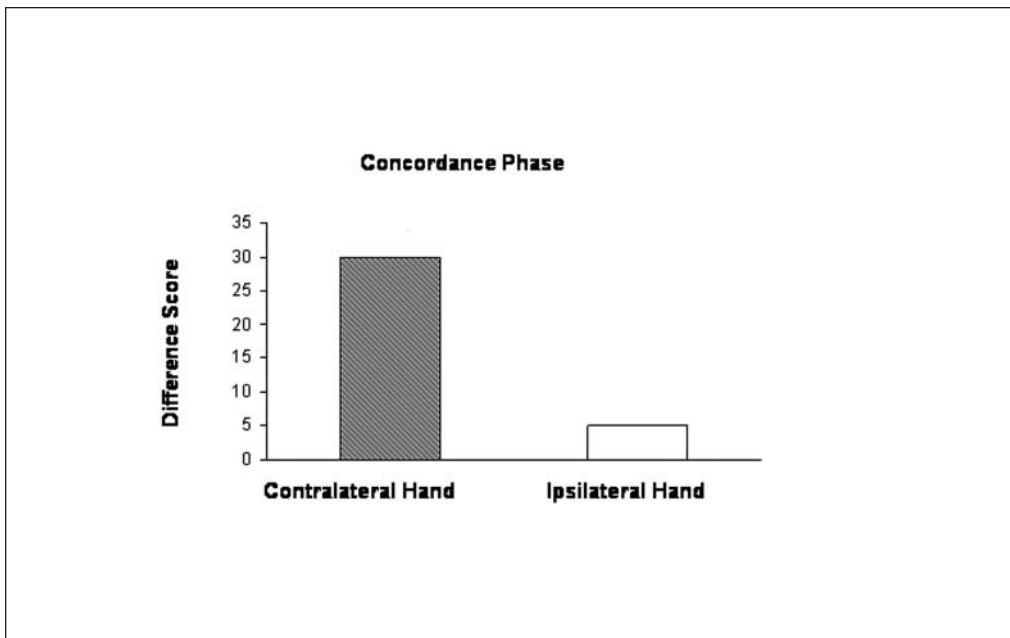


**Figure 1.** (A) Histogram of concordance phase (CP) values with bin widths of 20 units for the patient's contralateral hand pre- and post-deep brain stimulation (DBS). (B) Histogram of the mean CP value for the patient post-DBS (dotted line) compared to the mean CP value of a healthy control subject (dashed line). (C) Histogram of the mean CP value for the patient's contralateral (dotted line) and ipsilateral (dashed line) hand pre- and post-DBS.

than the ipsilateral hand.

The concordance phase variable for the contralateral hand is distributed around a mean value of approximately 32 with a standard deviation of 12 pre-DBS, near the 0 end of the scale that corresponds to a rigid swaying rhythm. The post-DBS mean, however, was significantly higher ( $142 \pm 18$ ) with substantial shifting toward the 180 end of

the scale that would reflect a repetitive pinching rhythm. A histogram illustrating the distribution of concordance phase in aggregate trials by the PD patient using the contralateral hand pre- and post-DBS is shown in Figure 1A. The concordance phase values of the contralateral hand post stimulation were still 21% less than the values for an age-matched control (Figure 1B). The concor-



**Figure 2.** Difference scores between the pre- and post-deep brain stimulation (DBS) concordance phase values of the patient's contralateral compared to ipsilateral hand.

dance phase values for the ipsilateral hand were substantially higher than those of the contralateral hand before VIM DBS and were not changed by the stimulation ( $164 \pm 8$ ). The post-DBS values for the contralateral hand were lower than either the pre or post-DBS values for the ipsilateral hand (Figure 1C).

Indeed, a comparison of the pre- and post-DBS concordance phase values of this PD patient's contralateral and ipsilateral hand with those of a control participant matched for age, gender, and hand preference revealed that the contralateral hand values are substantially less post-DBS in comparison to values of either hand of the control subject; however, the values for the ipsilateral hand of the PD patient and the hand of similar preference status for the control participant are similar (Figure 2).

The difference between the thumb and finger frequencies of maximum power within the 5-7 Hz tremor range, if of a statistically significant non-zero magnitude, would tend to support the

notion of oscillation mechanisms local to each digit or ones substantially modulated through independent signal transduction pathways after branching from a common remote site of origin. In the case study presented here the mean values of this difference at all sessions for both contralateral and ipsilateral hands had detectable non-zero magnitude but the standard deviations were too large to conclude that any were statistically different from zero. Interestingly, the contralateral side pre-DBS, where tremor is most pronounced, showed that the thumb-finger difference was very close to 0 and the standard deviation is very much smaller than is observed for all other combinations of lateral grouping and session chronology.

## DISCUSSION

We have presented the case of a patient with tremor predominant PD who had become refractory to medication but who then experienced tremor reduction and increased force control following

VIM stimulation. Force control substantially increased and tremor was reduced for the contralateral hand. The changes that occurred for the ipsilateral hand were minimal and may be attributed to practice and familiarity with the task. In all cases the values of force control variables of the ipsilateral hand were similar to those of a control subject. In addition there was no detectable tremor present in the ipsilateral hand. Thus, despite the progressive nature of PD there were no changes in tremor power or force control values during a span of 13 months following stimulation.

Our finding that stimulation of the VIM results in tremor reduction contralateral to the implantation site is consistent with previous research.<sup>5,6</sup> In this patient tremor was reduced to the level of a control subject in the contralateral hand and there was no detectable tremor in the ipsilateral hand.

Our previous research suggested that PD patients experience force control abnormalities that are present even after mathematically separating tremor from aggregate force control data.<sup>1</sup> These findings are consistent with other studies in which PD is reported to impair movements that require finger dexterity and hence finer cortical control.<sup>8,9</sup> However the relationship between basal ganglia degeneration and force control abnormalities is not well established. Neural modulation through stimulation of the subthalamic nucleus and the internal segment of the globus pallidus is effective for improvement of bimanual motor performance, maximum grip force production and temporal aspects of motor performance.<sup>7</sup> These authors suggest that stimulation may reduce the variability in force control such that the neural circuitry can operate in a non-pathological way.

In this case study we sought to examine unimanual force control prior to and following thalamic stimulation.

Our findings showed that stimulation of the VIM results in force control improvements of the contralateral hand. Despite these improvements, contralateral hand performance did not reach the level of performance of the ipsilateral hand.

No changes in the temporal component of the task were observed for either the contralateral or ipsilateral hand. This finding is consistent with the notion that VIM DBS does not affect motor symptoms such as bradykinesia that are associated with PD. The time required to complete the tracing task by the contralateral hand was greater by more than 50% when compared to the ipsilateral hand or to either of the control subject's hands. These findings are consistent with other data suggesting that following stimulation of the subthalamic nucleus PD patients were still more than 40% slower in completing tasks than are controls.<sup>10</sup>

In conclusion, the evidence presented suggests that the VIM DBS is an important site for reducing action tremor and improving force control in PD. In addition stimulation is associated with stable tremor and force control and coordination in PD. These data support a link between basal ganglia degeneration and force control.

## REFERENCES

1. Spirduso W, Francis K, Eakin T, Stanford C. Quantification of manual force control and tremor. *J Mot Behav.* 2005;37:197-210.
2. Volkmann J. Deep brain stimulation for the treatment of Parkinson's disease. *J Clin Neurophysiol.* 2004;21:6-17.
3. Forsberg H, Ingvarsson PE, Iwasaki N, et al. Action tremor during object manipulation in Parkinson's disease. *Mov Disord.* 2000;15:244-254.
4. Eakin T, Francis K, Spirduso W. Decoupling tremor and volitional force control factors in analyses of motor task performance. *Comput Statist Data Anal.* 2001;37:363-372



5. Ondo W, Dat Vuong K, Almaguer M, et al. Thalamic deep brain stimulation: effects on nontarget limbs. *Mov Disord.* 2001;16:1137-1142.
6. Putzke JD, Wharen RE, Wszolke ZK, et al. Thalamic deep brain stimulation for tremor-predominant Parkinson's disease. *Parkinsonism Relat Disord.* 2003;10:81-88.
7. Alberts JL, Elder CM, Okun MS, Vitek JL. Comparison of pallidal and subthalamic stimulation on force control in patients with Parkinson's disease. *Motor Control.* 2004;8:484-499.
8. Agostino R, Curra A, Giovannelli M, et al. Impairment of individual finger movements in Parkinson's disease. *Mov Disord.* 2003;18:560-592.
9. Vaillancourt DE, Slifkin AB, Newell KM. Inter-digit individuation and force variability in the precision grip of young, elderly, and Parkinson's disease participants. *Motor Control.* 2004;6:113-128.
10. Vaillancourt DE, Prodoehl J, Verhagen Metman L, et al. Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson's disease. *Brain.* 2004;127:491-504.