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Do Patient's Get Angrier Following STN, GPi, and Thalamic Deep Brain Stimulation

Adam P. Burdick, MD¹, Kelly D. Foote, MD¹, Samuel Wu, PhD⁵, Dawn Bowers, PhD³, Pam Zeilman, ARNP², Charles E. Jacobson, MS², Herbert E. Ward, MD⁴, and Michael S. Okun, MD^{1,2}

¹University of Florida Movement Disorders Center, Department of Neurosurgery, Gainesville, FL, USA

² University of Florida Movement Disorders Center, Department of Neurology, Gainesville, FL, USA

³ University of Florida, Movement Disorders Center, Department of Clinical and Health Psychology, Gainesville, FL, USA

⁴ University of Florida, Movement Disorders Center, Department of Psychiatry, Gainesville, FL, USA

⁵ University of Florida, Department of Epidemiology and Health Policy Research

Abstract

Objective—The objective of the study was to examine whether deep brain stimulation (DBS) of the subthalamic nucleus (STN), the globus pallidus internus (GPi), and/or the ventralis intermedius thalamic nucleus (Vim) was associated with making patients angrier pre to post-surgical intervention.

Background—Secondary outcome analysis of the NIH COMPARE Parkinson's Disease DBS trial revealed that participants were angrier and had more mood and cognitive side effects following DBS. Additionally blinded on/off analysis did not change anger scores. The sample size was small but suggested that STN DBS may have been worse than GPi in provoking anger. We endeavored to examine this question utilizing a larger dataset (the UF INFORM database), and also we included a third surgical target (Vim) which has been utilized for a different disease, essential tremor.

Methods—Consecutive patients from the University of Florida Movement Disorders Center who were implanted with unilateral DBS for Parkinson's Disease (STN or GPi) or Essential Tremor (Vim) were included. Patients originally implanted at outside institutions were excluded. Pre- and 4-6 month postoperative Visual Analog Mood Scales (VAMS) scores for all three groups were compared; additionally, pre- and 1-3 month scores were compared for STN and GPi patients. A linear regression model was utilized to analyze the relationship between the VAMS anger score and the independent variables of age, years with symptoms, Mini-mental status examination (MMSE) score, handedness, ethnicity, gender, side of surgery, target of surgery, baseline

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Corresponding Author: Michael S. Okun, MD Phone: (352) 273-5550 Fax: (352) 273-5575 okun@neurology.ufl.edu.

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Dementia Rating Scale (DRS) total score, baseline Beck Depression Index (BDI) score, micro and macro electrode passes, and years of education. Levodopa equivalent dosages and dopamine agonist use was analyzed for a potential impact on anger scores.

Results—A total of 322 unilateral DBS procedures were analyzed, with STN (n= 195), Vim (n=71), and GPi (n=56) making up the cohort. An ANOVA analysis was used to detect significant differences among the three targets in the changes pre- to post-operatively. Similar to the COMPARE dataset, at four months the only subscore of VAMS to reveal a significant difference between the three targets was the angry subscore, with GPi revealing a mean (standard) change of 2.38 (9.53), STN 4.82 (14.52), and Vim -1.17 (11.51) (p-value = 0.012). At 1-3 months postop, both STN and GPi groups were significantly angrier (p= 0.004), but there was no significant difference between the two groups. However, GPi patients were significantly more confused as compared to STN patients (p= 0.016). The linear regression model which sought independent explanatory variables revealed a relationship between the VAMS anger score and the surgical target and the disease duration. The mean changes for STN and GPi DBS pre- to post were 11.67 (p= 0.001) and 8.21 (p= 0.022) units more than those with Vim, respectively. For every year added of disease duration, the VAMS anger score increased by 0.24 (p= 0.022). For the GPi and STN groups, number of microelectrode passes was significantly associated with angry score changes (p= 0.014), with the anger score increasing 2.29 units per microelectrode pass. Independent variables not associated with the VAMS anger score included the surgery side, handedness, gender, ethnicity, education, age at surgery, MMSE, DRS, and BDI scores. Although the STN group significantly decreased in LED when compared to GPi, there was no relationship to anger scores. Similarly dopamine agonist use was not different between STN and GPi groups, and did not correlate with the VAMS anger score changes.

Conclusions—STN and GPi DBS for Parkinson's disease were associated with significantly higher anger scores pre- to post-DBS as compared to Vim for essential tremor. Anger score changes in STN and GPi patients seem to be associated with microelectrode passes, suggesting it may be a lesional effect. PD patients with longer disease durations may be particularly susceptible, and this should be kept in mind when discussing the potential of DBS surgery for an individual patient. Essential tremor patients who on average have much longer disease durations did not get angrier. The changes in anger scores were not related to LED change or dopamine agonist use. Whether the induction of anger is disease specific or target specific is not currently known, however our data would suggest that PD patients implanted in STN or GPi are at a potential risk. Finally, on closer inspection of the COMPARE DBS data VAMS anger scores did not change on or off DBS, suggesting that anger changes may be more a lesional effect rather than a stimulation induced one (Okun et al., 2009).

Keywords

Subthalamic nucleus; globus pallidus; ventralis intermedius nucleus; deep brain stimulation; anger; Parkinson's disease; tremor

1. INTRODUCTION

The utility and efficacy of deep brain stimulation (DBS) for addressing medication refractory motor symptoms and fluctuations in well selected Parkinson's disease (PD) patient cohorts has been well documented by multiple studies and multiple investigators (Benabid et al., 1989; Deuschl et al., 2006; Okun et al., 2009). The effects of DBS on mood and cognition however have been less carefully studied and therefore present a somewhat complex issue since PD is commonly associated with mood and cognitive dysfunction (Funkiewiez et al., 2004; Funkiewiez et al., 2006; Funkiewiez et al., 2003; Lang and Obeso, 2004a, b; Pilon et al., 2000; Rodriguez-Oroz et al., 2005; Rodriguez et al., 2005; Saint-Cyr et al., 2000). In the recently published randomized NIH COMPARE PD DBS

study, the subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS sites were compared on mood and cognitive variables (Okun et al., 2009). Interestingly, one secondary variable, the Visual Analog Mood Scale (VAMS) “angry” score, worsened in both surgical targets and this approached significance in the STN group (p -value = 0.027, noting that significance for this double primary outcome study was set at p -value = 0.025) (Okun et al., 2009). This study, similar to several others suggested that STN DBS was potentially implicated in anger, aggressiveness, and impulsivity (Bejjani et al., 2002; Frank et al., 2007; Funkiewiez et al., 2004; Sensi et al., 2004), with a higher total number of mood and cognitive adverse events in the STN group. This suggested the possibility of a target specific phenomenon.

The objective of the current study was to examine whether DBS of the STN, the GPi, and/or the ventralis intermedius thalamic nucleus (Vim) would be associated with anger when comparing pre to post-surgical intervention. The NIH COMPARE Parkinson's Disease DBS trial cohort was too small to draw any definite conclusions, so we endeavored to examine this question utilizing a much larger dataset (the UF INFORM database). We also included in the analysis a third surgical target (Vim) which is utilized for a different disease, essential tremor. This third target provided us with a different disease, and also different surgical target for comparison.

2. MATERIAL AND METHODS

Consecutive patients from the University of Florida Movement Disorders Center who were implanted with unilateral DBS for Parkinson's Disease (STN or GPi) or Essential Tremor (Vim) were included. Unilateral DBS is our standard protocol for both PD and ET patients, and patients are not offered a second side until following four to six months of medication and stimulation optimization. Patients originally implanted at outside institutions were excluded from the analysis. An ANOVA analysis was used to detect significant differences in Visual Analog Mood Scales (VAMS) scores among the three targets pre- to 4-6 month post-operatively; additionally, the same scores were compared for the GPi and STN groups at 1-3 months postop to detect early changes. The VAMS is a widely used validated tool used to measure 8 mood states (Afraid, Confused, Sad, Angry, Energetic, Tired, Happy, Tense) (Arruda et al., 1996; Arruda et al., 1999; Stern, 1997; Temple et al., 2004). A linear regression model was utilized to analyze the relationship between the VAMS anger score and the independent variables such as age, years with symptoms, handedness, ethnicity, gender, side of surgery, target of surgery, micro-and macroelectrode passes, and education. Also analyzed were mood variables, such as the Beck Depression Inventory (BDI) as well as cognitive variables, such as the Dementia Rating Scale (DRS) and the Mini-Mental Status Examination (MMSE). Chi-square tests or Fisher tests were used for testing the dependence between surgery target and categorical variables. Spearman correlation coefficients evaluated LED changes with VAMS anger score changes, and the Kruskal Wallis test was used to test whether continuous variables were different among surgical targets, and whether agonist use was related to VAMS anger score changes.

3. RESULTS

A total of 322 unilateral DBS procedures were analyzed, with STN ($n=195$), Vim ($n=71$), and GPi ($n=56$) making up the cohort. A summary of baseline statistics for each patient group is provided in Table 1. In general there were more right-handed patients, more people were implanted in the left hemisphere, and most of the cohort was Caucasian. The STN group had slightly more years of education, and the ET group expectedly had longer disease durations. There were no significant differences among all groups at baseline in MMSE, DRS, VAMS anger scores, or BDI scores.

The ANOVA analysis for pre- and post-operative values is summarized in Table 2, and shows the mean and standard changes seen between baseline and 4-6 months postoperative VAMS and BDI scores. The changes for anger at 1-3 months for GPi and STN patients were significant as a group ($p = 0.004$, not shown in a table), but they were not significantly different between the two groups ($p = 0.594$). (Table 2b) There was, however, a significant difference between the confusion scores between GPi and STN, with the former group having higher confusion scores. The anger changes continued to be significant at 4 months ($p < 0.0001$, not shown in a table), and similar to the COMPARE dataset, the only subscore of VAMS to reveal a significant change between the three targets was the angry subscore, with GPi revealing a mean (standard) change of 2.38 (9.53), STN 4.82 (14.52), and Vim -1.17 (11.51) (p -value = 0.012).

The linear regression model which sought independent explanatory variables revealed a relationship between the VAMS anger score and the surgical target and the disease duration. (Table 3) The mean changes for STN and GPi DBS pre- to post were 11.67 (p -value = 0.001) and 8.21 (p -value = 0.026) units more than those with Vim, respectively. For every year added of disease duration, the VAMS anger score increased by 0.24 (p -value = 0.022). In an analysis of the number of micro and macroelectrode passes and GPi and STN anger changes, microelectrode passes were significantly associated with VAMS anger score changes ($p = 0.014$), with the anger score increasing 2.29 units per microelectrode pass. Independent variables not associated with the VAMS anger score included the surgery side, handedness, gender, ethnicity, education, age at surgery, MMSE, DRS, and BDI scores.

Pre- and post-operative changes in levodopa equivalent dosages between the STN and GPi groups were different. GPi patients had a mean increase (pre- to post-operatively) of their levodopa equivalent dosage (LED) of 288.4, while STN patients had a mean decrease of 63.17 ($p = 0.007$). (Table 4) Further when examining dopamine agonist use there were no differences between the STN and GPi groups pre- to post-operatively ($p = 0.955$). (Table 4) Despite the difference in LED changes between the two groups, there was no relationship between LED changes and VAMS anger score changes (STN $p = 0.907$, GPi $p = 0.298$, or in both targets $p = 0.644$). Similarly, there were no differences in anger score changes among the 4 agonist categories ($p = 0.504$). (Table 5)

4. DISCUSSION

Our results revealed that STN and GPi DBS for PD were both associated with significantly higher anger scores pre- to post-DBS as compared to Vim DBS for essential tremor. Anger score changes in GPi and STN patients correlated to microelectrode passes, suggesting it may be a lesional effect. Interestingly unlike what we hypothesized, GPi DBS was also associated with post-DBS anger raising the question as to whether this phenomenon is not brain target specific. PD patients with longer disease durations were found to be particularly susceptible to post-DBS anger, and this finding should be kept in mind when discussing the potential of DBS surgery for individual patients with long histories of disease. Essential tremor patients, who on average have much longer disease durations, did not experience post-DBS anger. Finally, on closer inspection of the COMPARE DBS data, the VAMS anger scores did not change on or off DBS, suggesting that the anger change may be more lesional, and less stimulation induced. (Okun et al., 2009) GPi patients had higher confusion scores than STN patients at three months, and this difference was significant. GPi patients also had higher numbers of macroelectrode passes than STN patients ($p = 0.016$), so this difference in confusion could have been lesional a lesional effect or alternatively a selection bias (some of the patients selected for GPi outside the COMPARE trial may have been placed in a GPi group because of pre-operative cognitive issues). The confusion effects did not however, persist at 6 months post-DBS.

While DBS for PD and ET has been primarily utilized to address the motor manifestations of the respective diseases, the brain target regions for DBS have a plethora of associated non-motor (limbic and associative) circuitry (Alexander et al., 1986). The STN has been shown to have dorsolateral sensorimotor, medial limbic, and ventromedial cognitive-associative regions (Parent and Hazrati, 1995). Additionally STN DBS has been reported to be possibly causative in associative, limbic, and cognitive circuit problems seen post-DBS (Funkiewiez et al., 2003; Houeto et al., 2002; Jahanshahi et al., 2000; Krack et al., 2001; Mallet et al., 2002; Pilon et al., 2000; Saint-Cyr et al., 2000; Schneider et al., 2003; Schroeder et al., 2002). One interesting study demonstrating these effects was reported by Biseul and colleagues who observed that recognition of fear expressions was reduced post-STN DBS. They theorized this reduction was due to current diffusion into associative and limbic STN (Biseul et al., 2005). In a follow-up study utilizing 18 FDG PET, they documented correlations to right orbitofrontal cortex (Le Jeune et al., 2008). Similarly, it has also been reported that PD patients post-STN DBS may have difficulties recognizing both sadness and anger, and possibly even disgust (Dujardin et al., 2004; Schroeder et al., 2004). Indeed, direct recordings from human STN while patients viewed emotionally laden pictures has further implicated STN in emotional information processing (Brucke et al., 2007). The strong connectivity of STN to frontal cortical associative and limbic regions, and its connections to other ventral basal ganglia structures provide a theoretical basis for post-DBS mood changes such as the anger finding in our study. Much less information is known about the GPi, however it also has rich connectivity to the same circuitry potentially placing this brain structure as an at risk area to precipitate post-DBS mood changes (Sudhyadhom et al., 2007). One reason we theorized that GPi would have less emotional effects (e.g. less anger) is that the DBS lead is implanted into a larger more forgiving motor territory (458mm^3 versus 158mm^3) when compared to STN. One could, based on the observation of anger in both post-STN and post-GPi DBS and its relation to microelectrode passes, hypothesize that the effect was lesional rather than stimulation induced.

The idea of current spread as the underlying mechanism of DBS induced effects has been previously explored by several authors, but mostly in case reports or small case series. One very relevant case to our findings was that reported by Sensi et al. These authors described a single patient who post-bilateral STN DBS had acute episodes of explosive aggressive behavior that was associated with on-off trials of left sided only STN stimulation (Sensi et al., 2004). All four left sided STN DBS contacts on the device reproduced this phenomenon, and the authors argued based on imaging and programming that the lead was well placed into the intended dorsolateral sensorimotor STN. However, they speculated on the possibility that the current may have spread into medial non-motor STN, and that fibers of passage and/or neighboring structures may have been implicated and responsible for limbic manifestations (e.g. posterolateral and ventromedial hypothalamus, medial forebrain bundle, and periaqueductal gray matter). These areas have been previously reported as important for the expression of defensive rage behavior (Eichelman, 1971; Siegel and Edinger, 1983). Indeed another case report of presumptive stimulation induced intra-operative aggression was thought to be due to posterior hypothalamic spread (Bejjani et al., 2002).

A lesional effect resulting from the placement of the DBS lead may play an important role in the genesis of post-DBS anger. If anger is a function of post-DBS frontal lobe disinhibition, it may be reasonable to compare data from verbal fluency which is a common post-DBS induced adverse event characterized by a decrease in the speeded production of words. Virtually all studies comparing pre-surgical to post-surgical verbal fluency performance have detected a decrease following DBS (Dujardin et al., 2001; Funkiewiez et al., 2004; Okun et al., 2009; Saint-Cyr et al., 2000). The decline in verbal fluency post-STN DBS has been mostly attributed to a lesional effect, although there has been a smaller contribution recently documented and deriving from stimulation induced effects occurring particularly at

ventral DBS contact locations(Mikos et al., 2010; Okun et al., 2009). The most sobering recent finding was the measurement of verbal fluency on and off STN DBS in a carefully double blinded procedure. Post-DBS data revealed that the scores failed to change significantly, and this finding provided strong support for a lesional effect(Okun et al., 2009). Interestingly, in the same dataset, VAMS anger scores were observed off and on medications and there was no change essentially pointing to the strong possibility of a lesional effect underpinning post-DBS anger.

Medication effects can be a confounding factor for mood changes in DBS patients. A significant reduction in LED between the STN and GPi groups could have contributed to the changes seen in STN and GPi anger scores. In PD patients a reduction in agonist has been associated with a dopamine agonist withdrawal syndrome, which has recently been reported as a constellation of physical and mood effects.(Rabinak and Nirenberg). Similar effects may be seen post-DBS surgery. Verbal fluency and recognition of certain facial expressions have been reported to be affected by LED and dopamine agonists, so their potential relationship to anger deserves attention(Brusa et al., 2003; Gotham et al., 1988; Lawrence et al., 2007; Sprengelmeyer et al., 2003). In our series, the pre- and post-operative changes in levodopa equivalent dosages between the STN and GPi groups was different. However, despite these differences there was no relationship between LED changes or dopamine agonist changes and the VAMS anger score. Our findings therefore suggest another mechanism other than medication changes for the observed post-DBS anger.

Despite the interesting results, this study had several important limitations. These limitations included a lack of a non-DBS control group, the potential effect of medications, and the potential test-re-test practice effects, which may have masked a larger decline in some of the neuropsychological tests. Also it should be pointed out that although VAMS is an instrument that has been validated in neurodegenerative diseases and recently utilized as the outcome study for a major DBS trial, its validity in this population is unknown(Okun et al., 2009; Stern, 1996, 1999; Temple et al., 2004). Recently, Perozzo studied behavioral modifications and family interactions in 15 PD patients post STN DBS(Perozzo et al., 2001). From psychological interviews it was noted that during the postoperative period conflicts and stress led to aggressive behavior from caregivers towards the patient. These poorly studied family interactions may have in some way contributed to a state of anger, and this may have biased the study. Despite these limitations we feel the data from this study is reasonably accurate and is bolstered by the inclusion of a Vim DBS group which failed to significantly change pre-post DBS. Finally, whether a diminished verbal fluency post-DBS could also result in a frustration that contributes in some way to increased anger scores remains unknown(Ardouin et al., 1999; Castelli et al., 2006; Funkiewiez et al., 2004; Pillon et al., 2000; Saint-Cyr et al., 2000; Trepanier et al., 2000).

5. CONCLUSIONS

STN and GPi DBS for PD were associated with significantly higher anger scores pre- to post-DBS, as compared to Vim DBS for essential tremor. As the number of microelectrode passes the VAMS anger score increases, suggesting a lesional effect. PD patients with longer disease durations may be particularly susceptible, and this should be kept in mind when discussing the potential of DBS surgery for an individual patient. Essential tremor patients who on average have much longer disease durations did not get angrier post-DBS. The changes in anger scores were not medication related. Whether the induction of anger is disease specific or target specific is not currently known, however our data would suggest that PD patients implanted in STN or GPi are at a potential risk. Finally, on closer inspection of the COMPARE DBS data VAMS anger scores did not change on or off DBS, suggesting

that anger changes may be more of a lesional effect rather than a stimulation induced effect (Okun et al., 2009).

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Table 1

Summary Statistics of Baseline Variables

Variable		All Surgeries N=322	DBS Target			P-Value
			GP1 (n=56)	STN (n=195)	Vim (n=71)	
DBS Side	L	187 (58.1%)	31 (55.4%)	105 (53.8%)	51 (71.8%)	0.028
	R	135 (41.9%)	25 (44.6%)	90 (46.2%)	20 (28.2%)	
Handedness	L	33 (10.8%)		28 (15.6%)	5 (7%)	<0.0001
	R	272 (89.2%)	54 (100%)	152 (84.4%)	66 (93%)	
Gender	F	99 (30.7%)	16 (28.6%)	57 (29.2%)	26 (36.6%)	0.185
	M	222 (68.9%)	39 (69.6%)	138 (70.8%)	45 (63.4%)	
Ethnicity	NA	8 (2.5%)	1 (1.8%)	7 (3.6%)		<0.0001
	White	277 (86.0%)	50 (89.3%)	158 (81%)	69 (97.2%)	
	Black	3 (0.9%)	1 (1.8%)		2 (2.8%)	
	Hispanic	32 (9.9%)	4 (7.1%)	28 (14.4%)		
	Asian					
	Other	2 (0.6%)		2 (1.0%)		
Baseline Agonist	NA	92 (28.6%)	5 (8.9%)	16 (8.2%)	71 (100%)	0.972
	No	97 (30.1%)	21 (37.5%)	76 (39%)		
	Yes	133 (41.3%)	30 (53.6%)	103 (52.8%)		
Education (years)		14.75 (2.76)	14.56 (3.1)	15.15 (2.53)	13.79 (2.89)	0.0003
Years with Symptoms		15.14 (12.24)	12.61 (5.1)	10.77 (4.89)	28.53 (18.62)	<0.001
Age at Surgery		61.72 (10.1)	61.07 (6.95)	59.4 (9.36)	68.27 (11.26)	<0.0001
LED		731.03 (607.04)	1001.68 (586.91)	898.95(521.58)	NA	0.229
MMSE		28.25 (1.64)	27.98 (1.71)	28.43 (1.51)	27.98 (1.86)	0.143
DRS Total		136.29 (6.31)	136.19 (6.4)	136.66 (6.03)	135.29 (7)	0.381
Motor Score (off med)		41.83 (12.05)	43.55 (9.99)	42.77 (12.97)	37.9 (10.2)	0.008
VAM Angry Score		48.71 (9.94)	48.65 (7.45)	48.8 (10.72)	48.51 (9.79)	0.243
BDI Score		10.94 (6.12)	11.21 (5.46)	11.37 (6.48)	9.63 (5.66)	0.218
MicroPasses		3.61±1.12	3.53±1.09	3.64±1.14		0.581
MacroPasses		1.35±0.74	1.60±0.74	1.28±0.72		<0.0001

Table 2
Mean (SD) of Changes between pre- and 4 month postoperative BDI Scores and VAM Parameters.

Change (Post - Baseline)	All Surgeries	GPI	STN	Vim	P-Value
BDI Score	-3.57 (6.61)	-3.8 (5.97)	-4 (7.37)	-2.25 (4.86)	0.134
VAM Afraid	-4.41 (18.42)	-3.34 (16.59)	-4.61 (20.76)	-4.92 (11.54)	0.498
VAM Confused	0.46 (12.95)	2.11 (12.97)	0.18 (14.21)	-0.37 (8.01)	0.326
VAM Sad	-1.29 (15.31)	-0.13 (11.81)	-0.2 (14.82)	-5.81 (18.97)	0.851
VAM Angry	3.14 (13.26)	2.38 (9.53)	4.82 (14.52)	-1.17 (11.51)	0.012
VAM Energetic	2.05 (14.9)	3.19 (13.9)	1.98 (14.27)	1.12 (17.71)	0.519
VAM Tired	-4.76 (14.22)	-4.94 (12.99)	-5.91 (14.49)	-1.12 (14.26)	0.065
VAM Happy	5.56 (15.53)	7.51 (14.93)	4.61 (15.6)	6.42 (15.99)	0.460
VAM Tense	-10.16 (18.37)	-12.89 (19.35)	-8.63 (18.48)	-12 (16.8)	0.365

Table 2b

Mean (SD) for Earlier Changes of BDI Score and VAM Parameters.

Change (1-3 months - Baseline)	All Surgeries	GPI	STN	P-Value
BDI	-4.72±7.29	-4.29±5.61	-4.90±7.89	0.600
VAM Afraid	-2.23±19.74	1.43±20.14	-3.50±19.51	0.118
VAM Confused	1.83±15.30	6.33±15.11	0.27±15.11	0.016
VAM Sad	-0.62±14.83	3.18±14.04	-1.93±14.91	0.086
VAM Angry	3.01±14.03	5.25±15.74	2.22±13.35	0.594
VAM Energetic	2.30±14.78	3.78±15.50	1.79±14.54	0.294
VAM Tired	-4.68±14.77	-1.65±15.89	-5.73±14.27	0.165
VAM Happy	5.82±14.42	6.59±13.56	5.55±14.74	0.576
VAM Tense	-9.23±19.13	-9.92±22.40	-8.99±17.93	0.827

Table 3

Estimates of Parameters

Dependent	Parameter	Estimate	Standard Error	P-Value
VAM Anger Change	Surgery Side	Left	-1.89	1.98
		Right		0.342
	Handedness	Left	4.60	3.47
		Right		0.186
	Gender	F	-1.68	2.18
		M		0.442
	Ethnicity	White	0.73	9.95
		Black	-2.39	14.58
		Hispanic	0.38	10.33
	Target	GPI	8.21	3.67
		STN	11.67	3.55
		Vim		0.001
	Education (Years)	0.05	0.37	0.886
	Years With Symptoms	0.24	0.11	0.022
	Age at Surgery	-0.07	0.11	0.545
	MMSE	-0.44	0.74	0.550
	DRS Total Raw	-0.27	0.19	0.168
	Baseline Medical Off Motor Score	-0.08	0.10	0.427
	Baseline BDI Score	-0.09	0.16	0.574
Micro/Macro passes for GPI and STN only	Micro Passes	2.286406	0.918.87	0.014
	Macro Passes	-0.83363	1.431754	0.561

Table 4

Changes of LED and Agonist use.

Variable			All	GPI	STN	P-Value
LED			15.71 (678.29)	288.4 (617.81)	-63.17 (676.87)	0.007
Agonist	Baseline	4-month				
	NA		96 (38.25%)	21 (37.5%)	75 (38.46%)	0.955
	No	No	52 (20.72%)	12 (21.43%)	40 (20.51%)	
	No	Yes	8 (3.19%)	1 (1.79%)	7 (3.59%)	
	Yes	No	38 (15.14%)	8 (14.29%)	30 (15.38%)	
	Yes	Yes	57 (22.71%)	14 (25%)	43 (22.05%)	

Even excluding NA, the p-value for Agonist change is still not significant (p-value=0.885). NA = data missing.

Table 5

Kruskal Wallis test showing no significant anger score changes among agonist categories

Agonist	Baseline	4-month	Mean (SD) of VAMS Anger Score Change
	No	No	5.09 (13.95)
	No	Yes	1.13 (8.22)
	Yes	No	4.59 (13.55)
	Yes	Yes	7.56 (15.02)

p-value = 0.504