

The Influence of Bilateral Subthalamic Nucleus Deep Brain Stimulation on Impulsivity and Prepulse Inhibition in Parkinson's Disease Patients

Lucy Gee^{a,c} Heather Smith^a Priscilla De La Cruz^a Joannalee Campbell^{a,c}
Chris Fama^a Jessica Haller^a Adolfo Ramirez-Zamora^b Jennifer Durphy^b
Era Hanspal^b Eric Molho^b Anne Barba^b Damian Shin^c Julie G. Pilitsis^{a,c}

Departments of ^aNeurosurgery and ^bNeurology, and ^cCenter for Neuropharmacology and Neuroscience, Albany Medical College, Albany, N.Y., USA

Key Words

Deep brain stimulation · Subthalamic nucleus · Parkinson's disease · Impulsivity · Prepulse inhibition

Abstract

Background: At least 14% of Parkinson disease (PD) patients develop impulse control disorders (ICDs). The pathophysiology behind these behaviors and the impact of deep brain stimulation in a real-life setting remain unclear. **Objectives:** We prospectively examined the impact of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on ICDs in PD patients, as well as the relationship between impaired sensorimotor gaiting and impulsivity. **Methods:** Patients undergoing bilateral STN-DBS were assessed for ICDs preoperatively and 1-year postoperatively using a validated questionnaire (QUIP-RS). A subset of patients completed the Balloon Analogue Risk Task (BART) and auditory prepulse inhibition (PPI) testing. **Results:** Analysis revealed 12 patients had an improvement in score assessing ICDs ('good responders'; $p = 0.006$) while 4 had a worse or stable score ('poor responders'; $p > 0.05$). Good responders further exemplified a significant decrease in hypersexual behavior ($p = 0.005$) and binge eating ($p = 0.01$). Impaired PPI responses

also significantly correlated with impulsivity in BART ($r = -0.72$, $p = 0.044$). **Discussion:** Following bilateral STN-DBS, 75% of our cohort had a reduction in ICDs, thus suggesting deep brain stimulation effectively manages ICDs in PD. The role of impaired PPI in predisposition to ICDs in PD warrants further investigation.

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Introduction

Impulse control disorders (ICDs) such as pathological gambling, hypersexuality, compulsive shopping, binge eating, punding and dopamine dysregulation syndrome are recognized as 'behavioral addictions' that develop in at least 14% of PD patients, and can lead to devastating social, familial and financial consequences [1–3]. Unfortunately, the current treatment options for ICDs are restricted to decreases in dopamine agonists (DAs) [4, 5] or the addition of psychoactive medications [2], both of which have disadvantages. Due to such a paucity of treatments, alternative therapies for ICDs such as subthalamic nucleus deep brain stimulation (STN-DBS) have significant implications for PD [6].

Why ICDs develop in PD patients remains ill defined. There is some evidence that sensorimotor gating, as measured by prepulse inhibition (PPI), may be irregular in patients with PD, schizophrenia and obsessive compulsive disorder [7–10]. PPI is known to be disrupted in disorders with basal ganglia dysfunction due to a lack of midbrain dopamine [9, 10]. A common measure of sensorimotor gating is a startle response [9]. PPI can be induced when a weak sensory event preceding a strong startle-inducing stimulus reduces the magnitude of the startle response [11–13]. Abnormalities signify the inability to properly attend to or ignore environmental stimuli. Impaired PPI may lead to ICDs in certain PD patients.

There is mounting evidence that STN-DBS may also reduce ICD behavior in PD patients. Specifically, in a study by Lhommée et al. [3], STN-DBS ameliorated dopamine dysregulation syndrome in 4/4 patients, behavioral addictions in 17/17 patients and compulsive dopaminergic medication use in 9/9 patients. In their study, however, DA reduction was more dramatic than typically occurs in practice. This study aims to shed light on the role of deep brain stimulation in ICDs, as well as to examine the role of PPI in impulsivity secondary to PD.

Methods

Participants

Consecutive patients undergoing bilateral STN-DBS for treatment of PD were offered participation. Those who qualified for surgical treatment completed the Unified Parkinson's Disease Rating Scale (UPDRS) and neuropsychological testing as part of routine preoperative workup. Patients who did not improve more than 30% on CAPSIT ON/OFF medication testing were not considered acceptable candidates for surgery, as well as those who demonstrated dementia (DRS score ≤ 130) or significant cognitive impairment at baseline testing. Subjects who could not complete testing due to language barriers and/or dementia were excluded from participation in the study. Institutional review board approval for the study was obtained.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

After giving informed consent, participants completed an impulsivity questionnaire, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS), which was given within 1 month preoperatively and 1 year postoperatively to track changes in behavior. The QUIP-RS was specifically developed to analyze impulsive behaviors in the Parkinson's patient population – including both the screening and follow-up of impulsivity in PD patients [14]. The questionnaire was administered in the clinic with a research associate available for assistance (e.g. help filling out questionnaires if writing was difficult due to tremors).

Balloon Analogue Risk Task and PPI

A subset of patients consented to additional testing consisting of the Balloon Analogue Risk Task (BART) and auditory PPI. Both were performed preoperatively on medications. BART is a computer game validated to test impulsivity [15, 16]. The goal of the participant is to collect as much virtual money as possible by pumping up 30 balloons at a rate of 5 cents per pump. The more pumps, the more potential money they will earn; however, if the balloon pops, they will lose the money. At any point, they may choose to stop pumping and press 'collect \$\$\$', whereby the money will be safe while they complete the rest of the 30 balloons. The balloon randomly pops between 1 and 128 pumps. The two measurements included for analysis were the average adjusted pump count and the total number of explosions.

In PPI, to elicit the startle response, subjects were exposed to a strong startling tone (115 dB) in the presence and absence of a prestartle 'warning tone' (74 dB). The orbicularis oculi contractile response was concurrently recorded via EMG (Nicolet Viking Quest EMG Machine), and the response data was analyzed for maximal response per auditory stimuli. EMG activity (filter 80–2,500 Hz) was continuously recorded from the right orbicularis oculi and digitized (sampling frequency 1,000 Hz). The EMG continuous recording filters for PPI were: interview scope sweep 100 ms/div, sensitivity 0.2 mV/div, main scope sweep 10 ms/div, input sensitivity 30 μ V/div. PPI was assessed by measuring the reduction of the startle response. Patients with severe head tremors that interfered with EMG recordings were excluded, as well as those with hearing impairments. Auditory PPI results were correlated with the BART impulsivity results using Pearson's correlation analysis.

Results

Demographics

The mean age of our subjects at the time of surgery was 57.63 years (range: 34–73) with an average disease duration of 12.19 years prior to surgical intervention (range: 6–20). There were 10 male participants and 6 female participants. Table 1 outlines the demographics as well as the lead locations and programmed stimulation settings of patient devices.

QUIP-RS

Analysis of the QUIP-RS results showed that 12 patients had an improvement in ICD score ['good responders (GRs)'] while 4 had a worse or stable score ['poor responders (PRs)'; fig. 1] with no obvious demographic differences (see online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381558). The 12 GRs had a significant decrease in ICD score [preoperative 11.75 ± 2.62 to postoperative $M = 3.42 \pm 1.00$; $t(11) = 3.36$, $p = 0.006$], while the 4 PRs had insignificant increases in scores [preoperative 12.50 ± 5.55 to postoperative $M = 18.00 \pm 1.78$; $t(3) = -1.29$, $p = 0.288$] (fig. 1).

Table 1. Patient demographics

Patient	Gender	Age of onset, years	Age at surgery, years	Duration of PD at surgery, years	Lead location relative to MC, mm	Contacts	Programming settings (frequency, pulse width and voltage)	LED, mg	DA, mg	UPDRS-III	GR vs. PR
1	M	46	59	13	L: 11.75 left, 2.5 posterior, 4.71 inferior R: 11.68 right, 2.10 posterior, 4.07 inferior	L: C+, 2-, monopolar R: C+, 1-, monopolar	L: 140, 60, 3.5 R: 140, 60, 1.7	2,175	3	82	GR
2	M	43	59	16	L: 11.75 left, 2.17 posterior, 4.39 inferior R: 9.18 right, 3.26 posterior, 6.34 inferior	L: STN1, 2-, 0-, 1+; STN2, C+, 0-, interleaved R: C+, 2-, monopolar	L: STN1, 125, 90, 4.5; STN2, 125, 90, 3.5 R: 140, 60, 4.0	1,842.5	9	41	GR
3	M	50	60	10	L: 11.49 left, 1.11 posterior, 7.29 inferior R: 10.95 right, 1.70 posterior, 5.91 inferior	L: C+, 2-, monopolar R: C+, 1-, monopolar	L: 140, 60, 3.2 R: 130, 60, 2.3	1,100	0	31	GR
4	F	34	54	20	L: 10.96 left, 4.26 posterior, 4.39 inferior R: 11.43 right, 0.82 posterior, 3.90 inferior	L: C+, 1-, 2-, double monopolar R: C+, 2-	L: 140, 60, 3.3 R: 140, 60, 3.1	2,230	24	44	PR
5	M	43	58	15	L: 11.68 left, 3.92 posterior, 7.86 inferior R: 9.73 right, 3.29 posterior, 5.14 inferior	L: STN1: C+, 3-, 2-, STN2, C+, 1-, interleaved R: C+, 1-, monopolar	L: STN1, 125, 90, 4.0; STN2, 125, 60, 3.6 R: 140, 60, 3.1	940.5	0	34	GR
6	M	40	54	14	L: 12.35 left, 4.04 posterior, 6.56 inferior R: 9.41 right, 4.35 posterior, 6.84 inferior	L: C+, 3-, monopolar R: C+, 3-, monopolar	L: 170, 90, 3.2 R: 150, 80, 2.8	1,800	1.5	30	GR
7	M	54	63	9	L: 12.17 left, 2.22 posterior, 5.15 inferior R: 9.95 right, 3.76 posterior, 4.19 inferior	L: C+, 1-, monopolar R: C+, 0-, 1-, double monopolar	L: 140, 60, 3.5 R: 140, 60, 3.8	637.5	2	50	GR
8	F	55	69	14	L: 11.52 left, 2.60 posterior, 3.91 inferior R: 10.13 right, 2.26 posterior, 2.55 inferior	L: 1-, 2+, 1 bipolar R: 1-, 2+, 1 bipolar	L: 120, 100, 5.3 R: 100, 100, 5.5	857.5	0.375	43	GR
9	M	40	48	8	L: 11.14 left, 2.27 posterior, 7.59 inferior R: 9.14 right, 4.19 posterior, 7.04 inferior	L: C+, 3-, 2-, double monopolar R: 1+, 3-, 2+, bipolar	L: 140, 60, 3.9 R: 140, 60, 3.7	1,430	0	32	PR
10	F	45	57	12	L: 12.57 left, 0.67 posterior, 4.59 inferior R: 10.01 right, 2.22 posterior, 7.11 inferior	L: STN1: C+, 2-, STN2, C+, 3-, interleaved R: 3-, 2+, bipolar	L: ST1, 125, 60, 3.8; STN2, 125, 60, 2.0 R: 130, 90, 5.1	550	0	38	GR
11	F	40	50	10	L: 11.13 left, 2.09 posterior, 6.16 inferior R: 11.61 right, 2.67 posterior, 3.85 inferior	L: C+, 1-, monopolar R: C+, 2-, monopolar	L: 140, 60, 2.0 R: 140, 60, 1.7	4,500	0	55	GR
12	F	48	59	11	L: 14.29 left, 2.26 anterior, 3.34 inferior R: 10.02 right, 0.98 anterior, 2.90 inferior	L: C+, 0-, monopolar R: C+, 1-, monopolar	L: 140, 60, 1.6 R: 140, 60, 3.3	1,950	0	43	GR
13	M	60	73	13	L: 11.48 left, 1.10 posterior, 6.74 inferior R: 10.01 right, 1.82 posterior, 3.45 inferior	L: C+, 0-, monopolar R: C+, 0-, monopolar	L: 140, 60, 3.7 R: 140, 60, 2.1	1,048	1.5	26	PR
14	M	28	34	6	L: 10.97 left, 4.24 posterior, 5.56 inferior R: 8.61 right, 3.66 posterior, 5.83 inferior	L: STN1, C+, 0-, STN2, 1-, 2+, interleaved R: C+, 9-, monopolar	L: STN1, 125, 60, 2.8; STN2, 125, 60, 2.5 R: 125, 90, 3.6	1,240	12	31	GR
15	F	50	66	16	L: 10.80 left, 2.89 posterior, 5.53 inferior R: 10.56 right, 2.26 posterior, 5.59 inferior	L: STN1, 2+, 1-, STN2, C+, 3-, interleaved R: STN1: C+, 1-, STN2, C+, 3-, interleaved	L: STN1, 125, 60, 2.2; STN2, 125, 60, 1.3 R: STN1, 125, 60, 2.2; STN2, 125, 60, 1.5	1,496.5	0	16	PR
16	M	51	49	8	L: 12.86 left, 0.47 posterior, 6.59 inferior R: 9.48 right, 0.46 posterior, 4.20 inferior	L: STN1, C+, 2-, STN2, C+, 3-, interleaved R: STN1: C+, 2-, STN2, C+, 3-, interleaved	L: STN1, 125, 60, 4.3; STN2, 125, 90, 2.8 R: STN1, 125, 60, 4.5; STN2, 125, 60, 2.5	1,200	1	35	GR
								550	2	7	

STN 1 and STN 2 denote interleaved stimulation. See Discussion for explanation. LED, DA and UPDRS-III indicate pre- and postoperative values. LED = Levodopa equivalent dose.

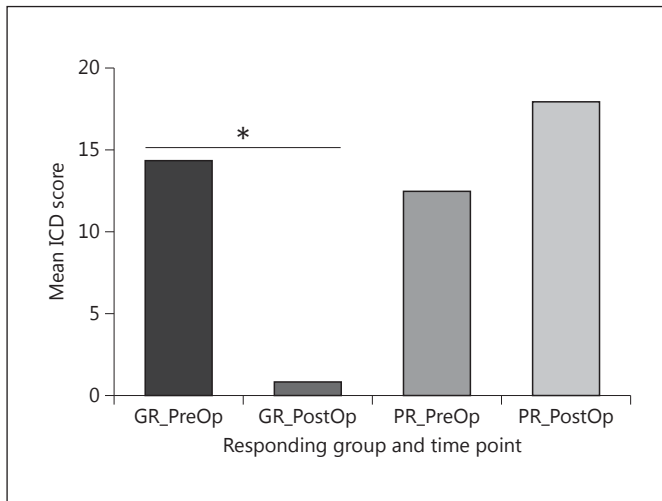


Fig. 1. Significant decrease of ICD score in GRs to STN-DBS in comparison to PRs (n = 16). PreOp = Preoperatively; PostOp = postoperatively. * p < 0.05.

When examining specific impulsive behaviors in GR patients, analyses revealed a significant decrease in hypersexual behavior [$t(11) = 3.55, p = 0.005$] and binge eating [$t(11) = 3.08, p = 0.01$] following STN-DBS (online suppl. fig. 1).

Treatment Differences

In an effort to determine differences between the GR and PR subsets, we examined the total daily levodopa equivalent dose and DA dose. There was a significant decrease in levodopa equivalent dose over time [$t(15) = 4.62, p = 0.0003$], but no difference between groups. Similarly there was no difference in total DA dose between groups ($p = 0.257$), lead location and/or stimulation parameters. Two of the 4 PRs had increases in DA versus 2 of 12 GRs. Of the 2 PRs who did not have DA increases, one patient had a preexisting abuse history of cocaine, amphetamines, marijuana and hallucinogens, suggesting addictive predispositions preceding PD. The other patient developed a unique sensory wearing-off phenomenon characterized by upper abdominal pain, which was only responsive to levodopa after surgery (despite continued programming and other medications). QUIP showed a de novo appearance of gambling, punning and hobbyism, and compulsive use of PD medication. In real life, he did not gamble or exhibit hobbyism.

Of note, 3 of 4 nonresponders had double monopolar settings, in comparison to 5 of 12 GRs. Only one PR had interleaved stimulation programming in contrast to 5 of

12 GRs. Monopolar stimulation was more commonly used in GR as compared to PR (82.4 vs. 17.6%, respectively).

PPI and Impulsivity

Analysis of the PPI and BART data from a separate subset of patients (n = 8) revealed a significant correlation between both overall PPI responses and total number of balloon explosions in BART ($r = -0.72, p = 0.044$), as well as responses to nonstartling auditory stimuli and total number of balloon explosions in BART ($r = -0.77, p = 0.026$; online suppl. fig. 2). There were also trends between responses to nonstartling stimuli and total number of balloon pumps in BART ($r = -0.67, p = 0.069$).

Discussion

Reduction in ICDs

We examined how STN-DBS affects impulsivity in PD as well as the possible influence of abnormal sensorimotor gating. We demonstrated that 75% of patients (12/16) had improvement in ICDs following surgery. This prospective study is the first to examine the effect of STN-DBS on ICDs prospectively in routine clinical settings.

Our findings are in agreement with the finding that STN-DBS coupled with aggressive DA reduction results in ICD reduction [3]. Other previous reports regarding the impact of STN-DBS on impulsivity in PD have been inconsistent [17–19]. One retrospective study showed a decrease in pathological gambling following bilateral STN-DBS, and while a general trend supporting this finding was found in our study, the change did not reach statistical significance [20]. Conversely, several case reports have documented the development of ICDs de novo following surgery [21–23].

In our study, there was a variable response observed to STN-DBS. In 2 PRs, the DA dose increased postoperatively. Why the 2 GRs with the DA increase did not see the same rise in ICDs suggests that it is not DAs alone that result in postoperative ICDs. When examining stimulation parameters in GRs versus PRs, there are many variables that may account for the differences in response. First, inadvertent stimulation of limbic and associated territories may account for increases in impulsivity. In contrast to delineation of striatal territories, the borderlines between the functionally segregated territories in the subthalamic nucleus overlap [24, 25]. With this model, one can argue overflow of stimulation into unintended areas of the subthalamic nucleus causing unwanted side effects.

Also 3 PR patients were stimulated with 1 or 2 medially located active contacts. Increased charge needed to control motor symptoms may have elicited impulsivity based on spreading of the current to the medial and anterior limbic areas.

Further, there were more double monopolar settings in PRs as opposed to more interleaving in GRs. Interleaved stimulation allows for two programs to be used in an alternating fashion on the same lead and has been shown to reduce side effects [26]. Theoretically, interleaving shapes the current to reduce spread, whereas double monopolar stimulation spreads the current. This finding suggests that interleaved stimulation might reduce ICDs in PD.

Mechanisms of Impulsivity

We also showed a significant negative correlation between impaired PPI and impulsivity on BART, suggesting an important disruption in sensorimotor information gating. Disorders with impaired PPI including PD all generate abnormalities in cortico-striato-pallido-pontine and cortico-striato-pallido-thalamic circuitry, which notably modulate PPI [8–10]. Therefore, neurodegeneration associated with PD is likely to affect both information gating and reward processing. PPI is known to be improved by DAs [9]. Furthermore, lower PPI is associated with increased distractibility [9], and impairments

have been linked to increased impulsivity and risk-taking behaviors [27]. Our study adds to the literature by showing that reduced PPI correlates with impulsivity in PD patients. However, despite the novelty of these present findings, we acknowledge small sample size and possible epiphenomenon. Future studies of PPI and impulsivity in PD, and more so how STN-DBS can impact PPI, are needed.

In conclusion, this study provides prospective data indicating STN-DBS improves ICDs in the majority of PD patients. Due to the lack of treatment options for ICDs in PD patients, these results have encouraging clinical implications.

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