SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

EFFECT OF SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION SURGERY ON IMPULSIVITY IN PARKINSON'S DISEASE PATIENTS

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DECLARATION

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INTRODUCTION

Impulsivity is a multifactorial construct that leads to inaptly deliberated actions or decisions, without having adequate forethought or consideration of the consequences[1-4]. These impulsive actions have a nature of choosing short term gains over long term ones leading to immediate gratification but long term pains[5]. Impulsivity can be a reflection of personality of a healthy individual or can be a component of various disorders ranging from pediatric behavioral disorders like Attention Deficit Hyperkinetic Disorder[6], psychiatric disorders like Bipolar disorder[7], antisocial personality[8] and substance abuse[9,10] to acquired brain injuries[11] and neurodegenerative disorders like Parkinson's Disease (PD)[12] and Frontotemporal dementia[12]. Though impulsivity seems to be an abstract construct, various self-assessment questionnaires (e.g. Barratts Impulsivity Scale (BIS) – 11)[13,14] and neuropsychological tasks {Balloon analogue risk task 15, Cued GoNoGo (GNG)[16,17] Iowa Gambling Task (IGT)[18,19]} mimicking real life decisions and conflicts have been developed and standardized to objectively measure it.

Increased Impulsivity in Parkinson's Disease (PD) has been fairly established as reflected upon by studies showing prevalence of impulse control disorders ranging from 2 to 31% in PD population[20-24]. Major risk factor is use of dopamine agonist and total levo-dopa equivalent daily dose (LEDD) in addition to younger age, male sex and family history of substance abuse and gambling, suggesting genetic/environmental factors also playing a role[21,24]. Increased impulsivity in PD patients have also been demonstrated by number of studies displaying impaired performance in the decision making situations and response inhibition simulated in neuropsychological tests such as IGT[25-36] and GNG[37] test respectively.

Subthalamic Nucleus - Deep Brain Stimulation (STN- DBS) is an accepted method of treating patients with PD who are experiencing incomplete relief of symptoms with medicines

or who have disabling side effects from medicines for PD[38-41]. STN-DBS achieves good control of motor symptoms of PD and thereby allows reduction of doses of drugs used in PD.

There is now a body of evidence that implicates STN to response inhibition and impulsivity[42-50]. It has been proposed that in PD, STN-DBS interferes with the normal function of the STN in situations of conflict. STN sends a "hold your horses" or "no go" signal to temporarily raise the response threshold to allow time for information accumulation before a decision is made and a response is produced[44]. Therefore, alteration of STN activity by STN-DBS in PD is predicted to result in fast impulsive responses when faced with conflict. However, reports are conflicting with some showing improvement[50], some worsening[48] and few showing no effect on impulsivity[47,49]. This variability in the cognitive responses post DBS in studies may be due to location specificity of contacts (i.e dorsal stimulation leads to improvement in motor responses in PD and spread of current of ventral DBS leads to alteration in limbic circuits responsible for impulsivity)[46,51] or may be secondary to reduction of dopaminergic drugs such as dopamine agonists or levodopa post DBS 50 or may reflect the methodological differences such as the type of response inhibition task used.

Hence in our study, we aim to assess the effect of STN DBS on impulsivity in PD patients using self-assessment questionnaires and computer based neuropsychological tasks. A major confounding factor while assessing impulsivity before and after DBS is the reduction in dopaminergic medications that is done after surgery, which can confound the independent effect of STN stimulation on impulsivity. In order to weed out this confounding factor we evaluated the effect of chronic STN-DBS stimulation (3 months) on both impulsive decision making and response inhibition in PD patients. We kept the dose of dopamine agonists (known to increase impulsivity) steady 3 months prior and 3 months after surgery, but allowed reduction of levodopa which is essential to control levodopa induced unwanted movements in PD. As dopamine agonists do not cause unwanted movements and their withdrawal after

prolonged use causes a syndrome called dopamine agonist withdrawal syndrome, they are not recommended to be withdrawn after DBS. Thus, we will be able to identify if STN DBS will improve impulsivity by itself without the confounding effect of dopamine agonist drugs withdrawal after surgery that may improve impulsivity.

REVIEW OF LITERATURE

In psychology, impulsivity is a tendency to act on a whim, displaying behavior characterized by little or no forethought, reflection, or consideration of the consequences[1]. Impulsive actions are typically "poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation that often result in undesirable consequences[2]," which imperil long-term goals and strategies for success[3]. Impulsivity can be classified as a multifactorial construct[4]. Thus, the construct of impulsivity includes at least two independent components: first, acting without an appropriate amount of deliberation, which may or may not be functional; and second, choosing short-term gains over long-term ones[5]. Abnormal patterns of impulsivity have also been noted in instances of acquired brain injury[11] and neurodegenerative diseases[12]. Though impulsivity seems to be an abstract construct, various self-assessment questionnaires (e.g. Barratts Impulsivity Scale (BIS) – 11)[13,14] and neuropsychological tasks (Balloon analogue risk task[15], Cued GNG[16,17], IGT[18 19]) mimicking real life decisions and conflicts have been developed and standardized to objectively measure it.

Impulse Control disorders, Impulsivity and Parkinson's Disease

Various studies has reported that prevalence of impulse control disorders (ICDs) in PD patients on dopamine agonist therapy ranges from 2%–31 %[20-24]. In study conducted by Weintraib et al.[21] among 3090 patients with treated idiopathic PD receiving routine clinical care in United States and Canada, an ICD was identified in 13.6% of patients. Based on multivariate analysis, author noted that the odds of having ICD while on dopamine agonist were 2 to 3 times higher. In addition, higher L-Dopa therapy was also associated with higher ICD odds ratio although evidence is less robust than that for dopamine agonist (odds ratio of 1.52). When Compared with patients without an ICD, those with an active ICD were younger and more likely to be unmarried, have more formal education, smoke cigarettes, report familial

gambling problems (both historical and current), and acknowledge alcohol abuse in first-degree relatives. Similarly, study done in our institute, by Sarathchandra et al.,[24] reported 31.6% of patients with atleast one ICD among 305 patients of PD, (based on validated criteria) and the risk of ICD was found to be significantly associated with the use of dopamine agonist therapy. In addition to other less robust risk factors similar to Dominion study were noted (Age of onset, smoking, total LEDD) with features of increased impulsivity on BIS 11 scores. ICD reflects the overt clinical manifestation of underlying elevated obsessionality, novelty seeking behavior and impulsivity. Growing number of studies have suggested that individuals with PD display impaired performance in the decision making situations simulated in neuropsychological tests such as IGT as shown in table1.

Anatomical correlate for IGT performance is originally considered to be ventromedial prefrontal cortex[18]. But various PET and functional neuroimaging studies have found deficits in limbic, orbitofrontal cortex and ventral striatal, the so called limbic loop circuit in PD without dementia with poor performances on IGT[12,19,27,29,33]. This dysfunction may be either due to hyperdopaminergic activity[12,50] or due to neurodegeneration in advanced PD[12].

Similar deficits have been noted in response inhibitions tasks in PD. Peter Manza et al.,[37] conducted a meta-analysis of studies with an aim to assess the deficits in Parkinson's disease by comparing them to healthy controls on tests of response inhibition (50 comparisons from 42 studies) and assess whether dopaminergic therapy improves deficits or not. Results from this meta-analysis in PD suggest that response inhibition deficits are least severe relative to controls when patients are in early-stages of PD and "on" dopaminergic medications. Deficits are more severe in later stages of PD "on" medications, and under medication withdrawal, regardless of disease duration.

Table 1 Summary of main studies of decision-making in PD[12]

STUDY	Year	Cases	Controls	Decision Making Paradigm	MAIN RESULTS
Czernecki et al. [25]	2002	23 PD,	28 controls	IGT	No benefit of levodopa administration on decision-making
Cools et al. [26]	2003	12 PD,	20 controls	CGT	Patients 'on' medication exhibited abnormal decision-making strategies
Thiel et al. [27]	2003	5 PD,	5 controls	IGT	No deficit on the IGT
Brand et al. [28]	2004	20 PD,	20 controls	GDT	Patients with PD preferred selecting cards from the disadvantageous decks
Perreta et al. [29]	2005	16 PD, 16 late PD,	19 controls	IGT	Both PD groups presented with learning impairments
Mimura et al. [30]	2006	18 PD,	40 controls	IGT	Patients with PD had deficits in decision-making
Pagonabarraga et al. [31]	2007	35 PD,	31 controls	IGT	More-severe deficits on the IGT associated with better general cognitive performance
Kobayakawa et al.[32]	2007	34 PD,	22 controls	IGT	Patients with PD selected more disadvantageous decks on the IGT and their SCR was lower than controls
Ibarretxe-Bilbao et al. [33]	2009	24 PD,	24 controls	IGT	Patients with PD had impaired decisionmaking on the IGT; volume in left lateral orbitofrontal cortex showed a slight correlation with IGT scores in the patient group
Euteneuer et al.[34]	2009	21 PD,	23 controls	IGT, GDT	Patients with PD were significantly impaired on the GDT, but not on the IGT
Delazer et al.[35]	2009	20 early PD, 19 PDD,	20 controls	IGT	Both PD and PPD groups demonstrated impaired decision-making under ambiguity; but only the PDD group was impaired on the PAG
Poletti et al.[36]	2010	30 PD,	25 controls	IGT	Patients with PD were unimpaired on the IGT

Impulsivity, STN-DBS and Parkinson's Disease

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), is a surgical technique now widely applied for the treatment of Parkinson's disease (PD) when dopamine replacement therapy fails to provide sustained relief of motor symptoms or induces drug-induced dyskinesias[38-41]. Though the exact mechanism of action of DBS is not well-established, it is known that stimulation disrupts[52] the increased synchrony and bursting activity in the β band (8–30 Hz) of the STN neurons[53].

Several reports have highlighted the development of new onset, often transient, impulse control disorders and deficits in response inhibition following STN stimulation[42,-50]. Smedling et al.,[42] described a patient with advanced Parkinson's disease who developed pathological gambling within a month after successful bilateral subthalamic nucleus (STN) stimulation. Pathological gambling disappeared after discontinuation of pergolide and changing the stimulation parameters.

Hershey et al.,[43] demonstrated in 24 PD patients, that STN DBS decreased patients' working memory performance under a high but not low memory load condition on the spatial delayed response [SDR]. On the GNG task, STN stimulation reduced discriminability on a high but not medium inhibition condition. Therefore, they concluded that STN stimulation reduces working memory and response inhibition performance under conditions of greater challenge to cognitive control despite significant improvement of motor function.

The study by Frank et al.,[44] also showed that STN DBS induced faster and less accurate responses in high conflict win-win decision trials on a probabilistic selection task based on their neurocomputional model. While on DBS, patients actually sped up their decisions under high-conflict conditions. This form of impulsivity was not affected by dopaminergic medication status. Instead, medication impaired patients' ability to learn from negative decision

outcomes. The authors hypothesized that the STN sends a 'No-Go' signal to the internal segment of the globus pallidus, which ultimately raises decision thresholds in the face of conflict. Stimulation may disrupt this signal, leading to inappropriately unchanged or even lowered thresholds in conflict situations.

Ballanger et al.,[45] went on to extend the observations provided by frank et al by trying to provide evidence that the STN may influence and prevent the execution of any response even during low-conflict decisions and they tried to identify the neural correlates of this effect. They measured regional cerebral blood flow during a GNG and a control (Go) task to study the motor improvement and response inhibition deficits associated with STN-DBS in patients with PD. They noted that STN-DBS impaired response inhibition, as revealed by an increase in commission errors in NoGo trials. These behavioral effects were accompanied by changes in synaptic activity consisting of a reduced activation in the cortical networks responsible for reactive and proactive response inhibition.

It is also hypothesized that the direct effect on STN DBS on response inhibition tasks may due to 1) stimulation of the cognitive sub territory of STN or the spread of stimulation to adjacent parts of the cortico-limbic circuits[46,51] or 2) the stimulation parameters such as current spread and electrode position[54,55] which can affect the outcome in cognitive tasks in PD patients. Various studies have looked into this hypothesis and tried to establish a clinical evidence.

Hershey et al.,[46] proposed that the location of the contacts used in deep brain stimulation could explain variability in the effects of deep brain stimulation of the subthalamic nucleus on response inhibition tasks. They hypothesized that stimulation affecting the dorsal subthalamic nucleus (connected to the motor cortex) would be more likely to affect motor symptoms of Parkinson's disease, and stimulation affecting the ventral subthalamic nucleus (connected to

higher order cortical regions) would be more likely to affect performance on a response inhibition task. They recruited 10 individuals with Parkinson's disease and bilateral STN-DBS with one contact in the dorsal and another in the ventral subthalamic region on one side of the brain. Patients were tested with a Go–No-Go task and a motor rating scale in three conditions: stimulation off, unilateral dorsal stimulation and unilateral ventral stimulation. Both dorsal and ventral stimulation improved motor symptoms, but only ventral subthalamic stimulation affected Go–No-Go performance, decreasing hits and increasing false alarms, but not altering reaction times. These results suggest that the ventral subthalamic nucleus is involved in the balance between appropriate selection and inhibition of prepotent responses in cognitive paradigms, but that a wide area of the subthalamic nucleus region is involved in the motor symptoms of Parkinson's disease.

The study from our institute by Mandali et al.,[51] also hypothesized that the position of electrode and stimulation current modulates impulsivity after STN-DBS. They built a computational spiking network model of basal ganglia and compared the model's STN output with STN activity in PD. Reinforcement learning methodology was applied to simulate IGT performance under various conditions of dopaminergic and STN stimulation where IGT total and bin scores were compared among various conditions. Untreated and medically- treated PD conditions showed lower total IGT scores (higher impulsivity) compared to HC (P<0.0001). The electrode position that happens to selectively stimulate the part of the STN corresponding to an advantageous panel on IGT resulted in de-selection of that panel and worsening of performance (P<0.0001). Supratherapeutic stimulation amplitudes also worsened IGT performance (P<0.001). Hence they concluded electrode position and stimulation current influenced impulsivity which may explain variable effects of STN DBS reported in patients.

York et al.,[54] conducted a standardized evaluation of the location of the DBS electrode tip and the active electrodes, the surgical trajectory through which they were placed, and their relation to change in neuropsychological scores (mental status, verbal memory, verbal fluency, and psychological measures) in 17 bilateral STN DBS patients using 6 month post-surgical magnetic resonance imaging data. Declines in mental status scores were related to electrodes that were more posterior-laterally placed within the frontal quadrant in either hemisphere or those located superiorly in the left hemisphere. Electrodes that were closer to the approximated STN and more superiorly located in the left hemisphere were associated with verbal learning declines at 6 months following surgery. In the right hemisphere, the electrodes that were located more in the lateral direction were related to verbal short-term memory declines; while for verbal long-term memory declines were found for electrodes located more posterior-laterally in the left hemisphere.

Witt et al.,[55] noted that electrode trajectories intersecting with caudate nuclei increased the risk of a decline in global cognition and working memory performance. Statistically, for every 0.1 ml overlap with a caudate nucleus, the odds for a decline >1 standard deviation increased by a factor of 37.4 (odds ratio, confidence interval 2.1–371.8) for the Mattis Dementia Rating Scale and by a factor of 8.8 (odds ratio, confidence interval 1.0–70.9) for the backward digit span task. Patients with subthalamic nucleus–deep brain stimulation who declined in semantic verbal fluency, Stroop task and the backward digit span task performance showed a position of the active electrode outside the volume built by the active electrodes of stable performers. Passage of the chronic stimulation lead through the head of the caudate increases the risk of global cognitive decline and working memory performance after subthalamic nucleus–deep brain stimulation in Parkinson's disease. Therefore, they concluded that the electrode path should be planned outside the caudate nuclei, whenever possible, laying stress on the importance of precise positioning of the active stimulating contact within the

subthalamic volume to avoid adverse effects on semantic verbal fluency and response inhibition.

Effect of STN stimulation on Iowa Gambling Task was also assessed in few studies with variable results. Some showed no effect[47,49], some showed decreased effect[50] and some an increase in IGT scores[48]. Czernecki V et al.,[47] aimed to analyze the effect of STN stimulation on motivation and reward sensitivity using Apathy Scale, Stimulus-Reward Learning, Reversal, Extinction, and Gambling tasks in 18 PD patients treated with bilateral STN DBS and comparing it with 23 matched patients undergoing long term treatment with levodopa (‘‘on’’ and ‘‘off’’ conditions). Apathy decreased under both STN stimulation and levodopa treatment, whereas explicit and implicit stimulus reward learning and IGT scores remained unchanged. Hence they concluded that bilateral STN stimulation in PD patients does not necessarily have a negative effect on motivation and reward sensitivity and can even improve apathy provided patients have been appropriately selected for neurosurgery.

Omaya G et al.,[49] assessed the acute effect of STN DBS on IGT in 16 advanced PD patients preoperatively and 2to 4 weeks postoperatively and compared them with 16 controls. They noted that total IGT score did not differ before and after surgery in on-stimulation or off-stimulation, but DBS patients tended to perform worse in the on-DBS session compared to off-DBS session (P ¼ 0.019) only in the last block of the task. The IGT score did not correlate with levodopa equivalent dose or performance on the measures of executive function, but did correlate with self-reported depression symptoms, and active contact of stimulation. They concluded that bilateral STN-DBS may affect decision-making in acute post-operative stage.

Castriole A et al.,[50] investigated the effects of STN DBS on IGT scores in pre and post surgery in PD patients. They compared PreDBS medication OFF and PreDBS medication ON state scores with PostDBS medication OFF-Stimulation OFF and Post DBS medication OFF stimulation OFF after 3 months respectively. They noted significant improvement in IGT score

and total IGT scores post DBS as compared to scores prior to surgery. No difference in scores was noted. PD medication ON vis a vis PD medication OFF groups. These findings suggest significant improvement in decision making Post DBS either due to significant decrease in dopaminergic medication was noted to reduce by 74%.

Evens et al., [48] compared 33 PD patients treated with DBS-STN under best medical treatment (DBS-on, medication-on) to 33 PD patients without DBS, but optimized pharmacological treatment and 34 age-matched healthy controls. They then investigated DBS-STN effects using a postoperative stimulation-on/ -off design. The task set included a delay discounting task, a task to assess changes in incentive salience attribution, and the Iowa Gambling Task. The presence of PD was associated with increased incentive salience attribution and devaluation of delayed rewards. Acute DBS-STN increased risky choices in the Iowa Gambling Task under DBS-on condition, but did not further affect incentive salience attribution or the evaluation of delayed rewards.

This variability in the cognitive responses post DBS in studies may be due to location specificity of contacts (i.e dorsal stimulation leads to improvement in motor responses in PD and spread of current of ventral DBS leads to alteration in limbic circuits responsible for impulsivity) or may be secondary to reduction of dopaminergic drugs such as dopamine agonists or levodopa post DBS or may reflect the methodological differences such as the type of response inhibition task used. Hence in our study, we aim to assess the effect of STN DBS on both impulsive decision making and response inhibition in PD patients using self-assessment questionnaires (BIS-11) and computer based neuropsychological tasks (IGT and GNG) with an effort to weed out the confounders in the previous studies.

AIMS AND OBJECTIVES

1) To compare the performance in impulsive decision making and response inhibition tasks in PD patients before and after STN-DBS to examine the effects of STN stimulation on impulsivity

2) To compare impulsivity in PD patients who underwent STN-DBS (PD-DBS) with medically treated PD patients who are matched with the surgical group for disease severity and treatment characteristics.

MATERIALS AND METHODS

Study design and setting

The present study conducted is prospective cohort study carried out in PD patients attending the Movement disorders clinic of the Comprehensive Care Center for Movement Disorders, Department of Neurology, from 2015 to 2017 at Sree Chitra Tirunal Institute for Medical Sciences and Technology, which is a tertiary referral centre in South India with specialized neurology services. All subjects gave written informed consent and the study was approved by the Ethics Committee of the hospital.

Subject selection

Subjects enrolled in the study were divided into PD-DBS group and PD- medical group, which were defined as follows

PD-DBS group: PD patients attending the Movement disorders clinic of the Comprehensive Care Center for Movement Disorders, Department of Neurology, SCTIMST and selected by the movement disorder team who underwent DBS surgery between 2015 and 2017.

PD-medical group: Medically treated PD patients who are matched with the surgical group but cannot undergo STN-DBS surgery because of medical comorbidities that don't allow surgery or financial constraints that limit surgical choice

Inclusion and exclusion criteria for each group

PD-DBS

Inclusion criteria:

- Age > 30 years

- PD duration >4 years with motor fluctuations/ dyskinesias and selected to undergo DBS

Exclusion criteria:

- Mini Mental State Examination (MMSE)< 24[56,57], Becks depression inventory (BDI) score of >25[58,59,60]
- Patients in whom dopamine agonist is planned to be reduced after DBS because of pre operative side effect of dopamine agonist use (presurgical impulse control disorder)

PD-medical

Inclusion Criteria

- Age > 30 years
- duration >4 yrs with motor fluctuations/ dyskinesias and selected to undergo DBS but cannot undergo STN-DBS surgery because of medical comorbidities that don't allow surgery or financial constraints that limit surgical choice

Exclusion Criteria

- MMSE < 24[56,57], Becks depression inventory score of >25[58,59,60]
- Patients in whom dopamine agonist is planned to be reduced because the side effect of dopamine agonist use

Recruitment

Recruitment of patients was done by the principal investigator and co-principal investigators. PD patients were screened for eligibility for STN-DBS by the movement disorders team. Patients who are eligible and undergo surgery will form PD-DBS group and those who meet inclusion criteria but do not undergo surgery formed PD medical group.

Data collection

Subjects after enrollment in study underwent following evaluations:

For PD-DBS group

Day 1. Screening and neuropsychological testing including- MMSE[56,57] (for cognitive ability), Beck's Depression Inventory[58,59,60] (for depression), modified Minnesota Impulsive Disorders Interview[61] (mMIDI, for impulse control disorders), Barratt Impulsivity Scale[13,14,63] and Apathy Scale[64] (for apathy) which were done on an outpatient basis, while the patient was taking his/her routine medications (drug ON).

For PD-DBS patients, further assessments took place during the one week prior to STN-DBS surgery while patient was admitted in hospital.

Day 2. A 12 hour (overnight) withdrawal of all dopaminergic drugs is done as part of routine pre-operative assessment to assess the OFF medication motor disability {Unified Parkinson's Disease Rating Scale (UPDRS)}. During this time, computerized tasks of impulsive decision making, the Iowa Gambling Task[18,19] and response inhibition[16,17] (Go No Go task) were also administered. The IGT is a validated measure of decision making in which subjects have to maximize profits and avoid losses while drawing cards one by one from four identical decks. A computerized version of IGT was used (Millisecond Software, LLC, Washington, USA). Subjects are allowed 100 draws. Two decks will be advantageous (net gain) and two decks will be disadvantageous (net loss). Total score is calculated as number of draws from advantageous decks minus number of draws from disadvantageous decks. Block scores were calculated for each block of 20 draws to analyze learning of the test. GNG rest is a validated measure of response inhibition. A computerized version (Millisecond Software, LLC, Washington, USA) was used which contains 250 trials. Subjects have to press a button when

shown a go cue, and withhold from pressing when shown a No Go cue. Errors of commission, errors of omission and mean reaction times were measured.

Day 3.The tasks were administered once more with the patient on his usual dose of dopaminergic drugs (drug ON).

Day 4. Three months after surgery (as it takes 3 months to get optimal stimulation effect) patients were reassessed with MMSE, Apathy scale, mMIDI and Barratt Impulsivity Scale. This is because apathy may worsen after STN-DBS and may affect performance on IGT. IGT and GNG was administered again in two conditions 1) DBS-stimulator ON, taking regular dose of drugs and 2) DBS stimulator ON and medications OFF (withheld overnight).

So in the DBS group, the effect of medication before surgery (testing medication OFF vs. with medication ON) and the effect of surgery (testing before surgery medication OFF with after surgery stimulation ON, medication OFF) was studied.

For PD medical group

Day 1 is the same as for DBS group. After screening tests, the eligible subjects underwent the computerized tests next day morning with medication held overnight (Medication OFF) and while taking routine dose of medications (medication ON).

Day 2 is 3 months later when they were retested again with medication OFF and medication ON.

Comparison of PD DBS and PD medical groups in OFF allowed us to compare whether patients undergoing DBS have more impulsive decision making.

Comparison of medical group twice allowed us in testing whether there is a learning effect of doing the same computerized tasks twice which may be the reason why performance in second testing may be better than first after surgery.

Clinical data regarding age of onset, duration of illness, details of drug therapy, clinical examination and UPDRS scores were collected from the patient and hospital records. Levodopa equivalent daily dosages of drugs were calculated using the formula: 100mg of regular L-DOPA =133 mg of 12 controlled release L-DOPA, =1mg of pramipexole, =5mg of ropinirole, =1mg of rasagiline, =100mg of amantadine, =0.33 x L DOPA dose of entacapone[65]. No additional investigations or treatment modifications was done as part of this study. All tests were conducted at the Comprehensive Care Centre for Movement Disorders by the principal and co-principal investigators.

DATA ANALYSIS

Data was be analyzed by the statistician of the institute. Primary outcome parameters were the difference between pre and post-operative 1) IGT scores and 2) Errors of commission and mean reaction time in GNG. Paired t-test were used to identify difference between scores in the 2 conditions pre op medication ON, pre op medication OFF, to study the effect of drugs on impulsivity and between preop drug On and post op stimulation ON drug ON, to assess the effects of surgery.

Repeated measures ANOVA were used to compare the scores in the 2 visits in the medical groups and the preop medication On and post Op DBS ON medication On scores. All data was handled with care to maintain patient confidentiality, using study code. Records were maintained in both computer and paper formats and solely under custody of study investigators. All statistical analyses was performed using the SPSS statistical software package (release 16.0, SPSS Inc.; Chicago,Ill).

RESULTS

A total of 30 PD patients who underwent DBS surgery were recruited in the PD-DBS group and 25 medically treated PD patients with motor fluctuations, matched with surgical group, were included in PD-MEDICAL group after informed consent.

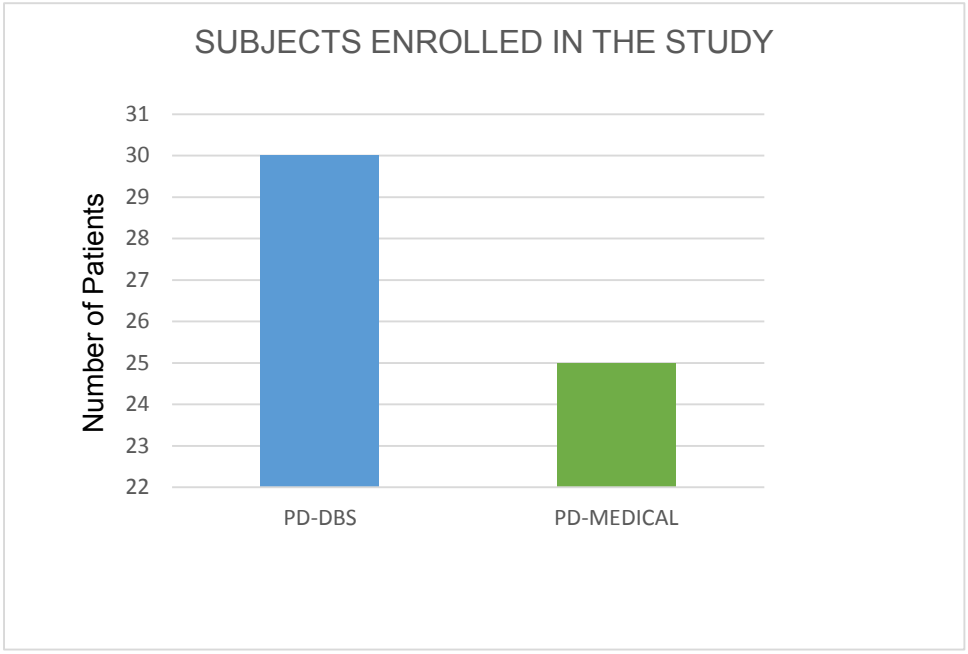

FIGURE 1 showing number of subjects enrolled in each study group

Demographic characteristics

Comparing age, a significant difference was noted between PD-DBS subjects (M=54.47 years, SD=6.79) and PD-Medical subjects (M=46.56 years, SD=8.95); t (53)=3.722,p=0.000.

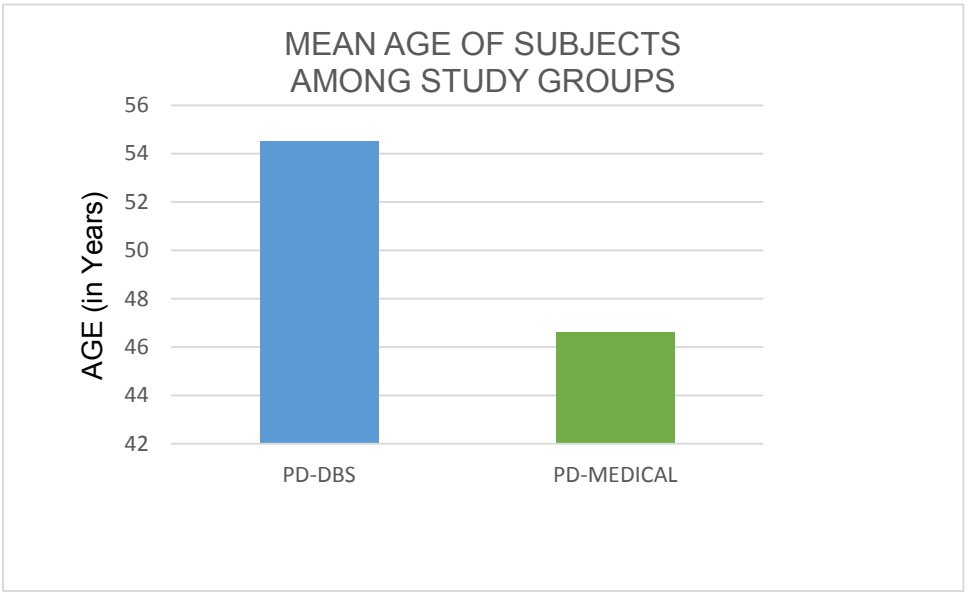

FIGURE 2 Comparing the mean age among study groups

Out of 30 subjects in PD-DBS group, 19 were male and 11 were female. In PD-Medical group, 8 were female and 17 were male out of 25

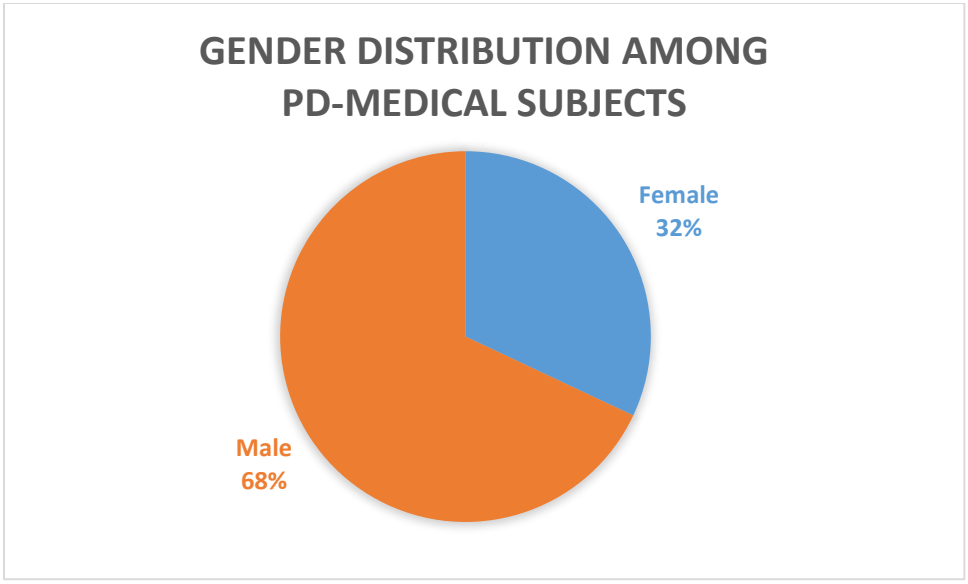

FIGURE 3 showing the gender distribution among PD-Medical group

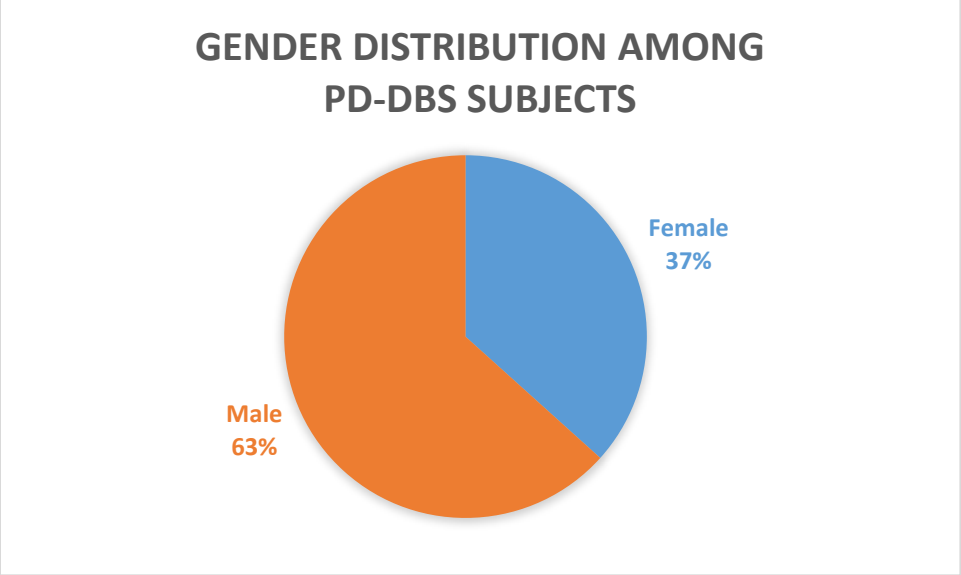

Figure 4 showing the gender distribution among PD-DBS group

A chi square test was performed and no significant differences were noted between gender among cases and controls. X^2 (1,N=55)=0.131, p =0.717

No significant difference was noted in the age of onset of PD between PD-DBS (M=10.93,SD=4.29) and PD-Medical group (M=9.44,SD=3.73); t(53)=1.36,p=0.179

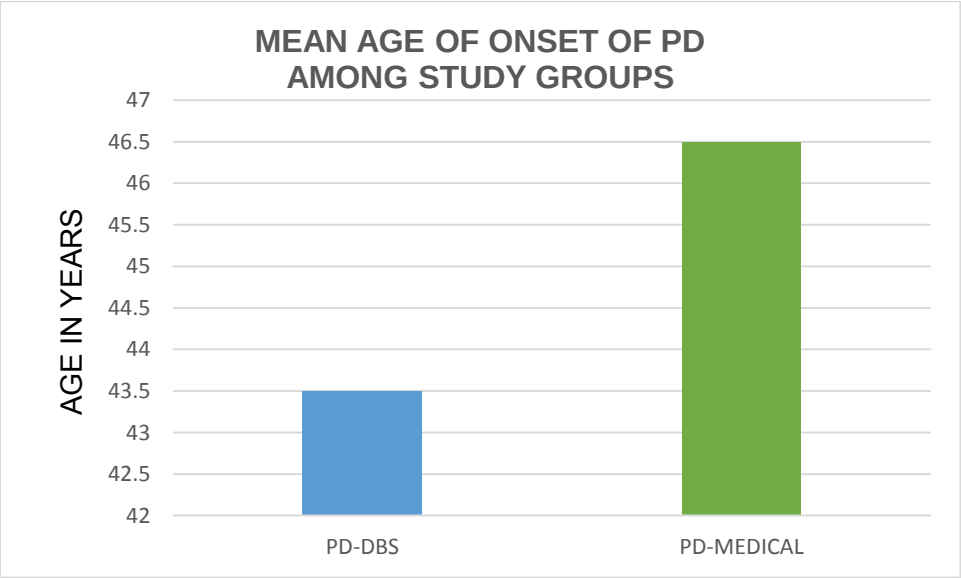

FIGURE 5 showing mean age of onset of PD among study groups

The duration of PD between PD-DBS (M=10.93,SD=4.29) and PD-Medical group (M=9.44,SD=3.73) was noted to be not statistically significant t(53)=1.36,p=0.179.

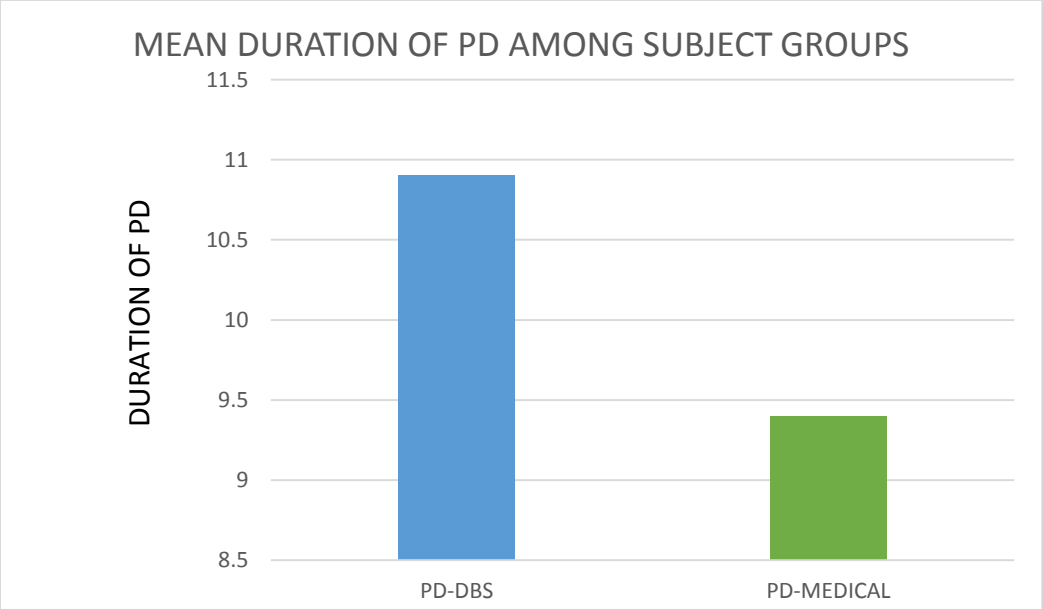

FIGURE 6 showing mean duration of PD among study subjects

Mean total LEDD in PD-DBS group was 1012.3 mg with SD=347.2 and in PD-Medical group was 743.9mg with SD=264.4. The difference was noted to be statistically significant t(53)=,p=0.003. Similarly, significant difference was noted in the mean total LEDD within PD-DBS group, before surgery (M=1012.3,SD=347.2.) and after surgery (M=612.50,SD=270.7); which was statistically significant t(53)=,p=0.00

Fifteen patients received pramipexole in PD-DBS group with mean dose of 2.65mg. There was no change in the dose of pramipexole after surgery in PD-DBS group. Thirteen patients in PD-Medical were on pramipexole with mean dose of 2.65mg. There was no statistical difference in pramipexole dose between PD-DBS (M=2.65, SD=1.64) and PD-Medical group (M=2.65, SD=1.25); t(53)=, p=0.993

Three patients received ropinorole in PD-DBS group with mean dose of 4.3mg. There was slight change in the dose of ropinorole after surgery in PD-DBS group with 2 out of 3 being

continued on ropinorole with mean dose of 3.3mg. This difference was not statistically significant. Four patients in PD-Medical were on ropinorole with mean dose of 1.88mg. There was no statistical difference in ropinorole dose between PD-DBS (M=4.3, SD=2.88) and PD-Medical group (M=1.88, SD=0.85); p=0.272

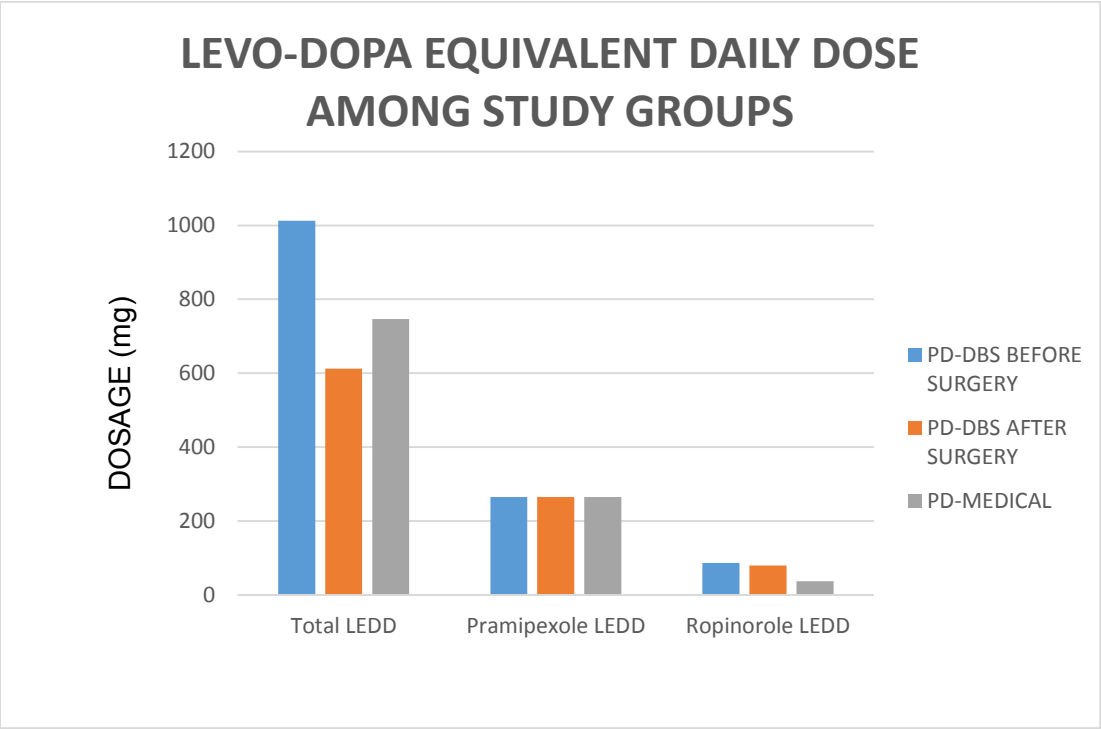

FIGURE 7 showing Levo-dopa equivalent daily dose among study groups

No significant differences were noted in BDI, Apathy, mMIDI and BIS scores between PD-DBS group and PD Medical group. Also within PD-DBS, before and after surgery, there were no significant differences between BDI, Apathy and BIS scores as shown in table. However, 5 patients were positive for mMIDI scores in PD-DBS group before surgery. After surgery, only 1 subject was positive ($p<0.05$) which was statistically significant.

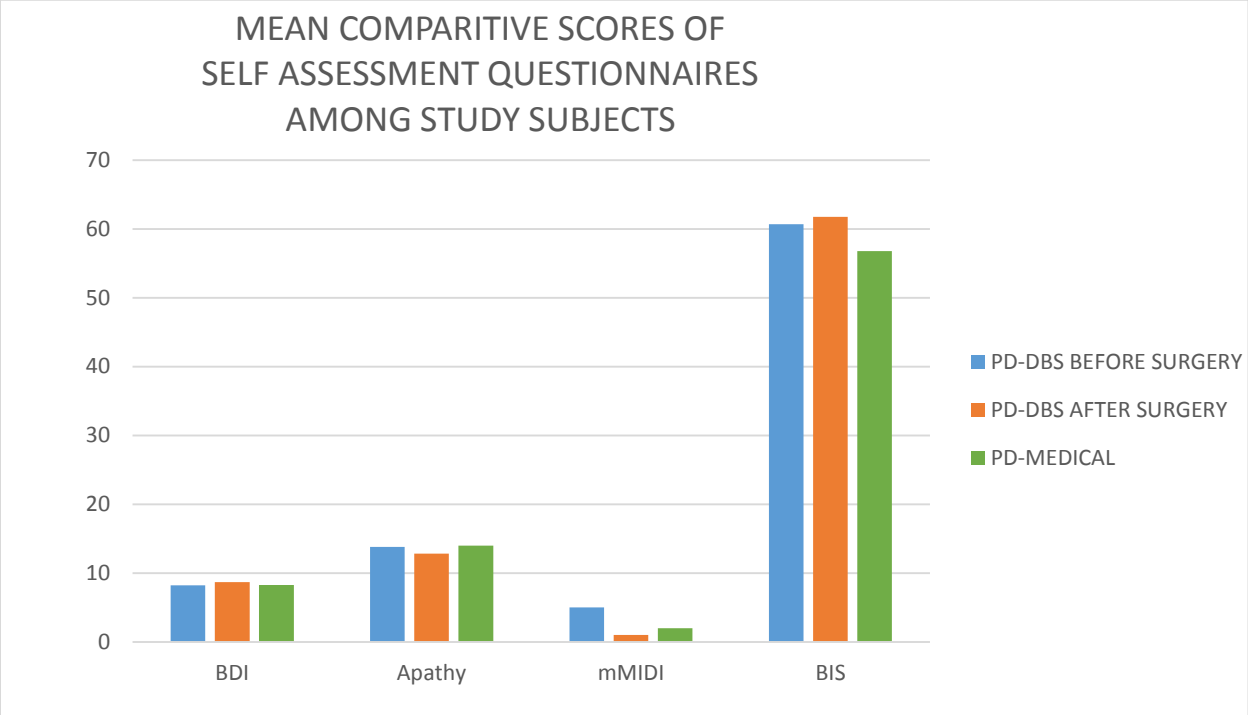

FIGURE 8 showing mean comparative scores of self-assessment questionnaire among study groups

TABLE 2 BASELINE CHARACTERISTICS OF SUBJECTS ENROLLED IN STUDY

	PD-DBS		PD-MEDICAL
	Before Surgery	After Surgery (3 months)	On VISIT 1
Number	30		25
Age (Years)	54.47 +/- 6.79		46.56 +/- 8.95 (p=0.00)[A]
Sex (F:M)	11:19		8:17 (p=0.717)[B]
PD Duration (years)	10.93 +/- 4.29		9.44 +/- 3.73 (p=0.179)[A]
Age of onset of PD (years)	43.53 +/- 7.79		46.56 +/- 8.95 (p=0.186)[A]
UPDRS III OFF scores	48.56 +/- 13.64	12.30 +/- 7.42 (p<0.05)[C]	41.80 +/- 13.05 (p=0.07)[A]
UPDRS III ON scores	10.10 +/- 6.24	9.6 +/- 5.86 (p<0.05)[C]	10.20 +/- 5.27 (p=0.950)[A]
LEDD (mg)	1012.27 +/- 347.20	612.50 +/- 270.68 (p=0.00)[C]	743.96 +/- 264.46 (p=0.003)[A]
Pramipexole (n)	15	15	13
Pramipexole dose (mg)	2.65 +/- 1.64	2.65 +/-1.64 (t=0)	2.65 +/- 1.25 (p=0.993)[A]
Pramipexole (LEDD) (mg)	265.00 +/- 116. 41	265.00 +/- 116. 41 (t=0)	265.38 +/- 124.80 (p=0.993)[A]
Ropinorole (n)	3	2	4
Ropinorole dose (mg)	4.33 +/- 2.88	3.33 +/- 3.05 (p=0.225)[C]	1.88 +/- 0.85 (p=0.27)[A]
Ropinorole (LEDD) (mg)	86.66 +/- 57.73	80.00 +/- 69.28 (p=0.423)[C]	37.50 +/- 17.08 (p=0.27)[A]
BDI	8.23 +/- 3.65	8.70 +/- 5.93 (p=0.625)[C]	8.24 +/- 4.46 (0.995)[A]
Apathy	13.8 +/- 5.73	12.83 +/- 4.79 (p=0.296)[C]	13.96 +/- 6.19 (p=0.921)[A]
mMIDI (n = subjects with positive screening)	5	1 (p<0.05)	2
BIS	60.70 +/- 7.94	61.73 +/- 6.07 (p=0.322)[C]	56.76 +/- 8.46 (p=0.08)[A]

A = Independent student t test

B = Chi square test

C = Paired student t test

Cued GoNoGo TEST

Cued GoNoGo test was performed in 26 of the 30 subjects in PD-DBS group before and after surgery in OFF and ON state. The mean value of parameters obtained from the test are shown in the table 3.

TABLE 3 showing mean values of variables assessed in Cued GoNoGo test among PD-DBS group

CUED GO NO GO	PD-DBS				P value
	Before Surgery (n=26)		After Surgery (n=26)		
	OFF State	ON State	OFF State	ON State	
Errors of commision[C]	0.77 +/- 1.142	2.31+/- 4.077	0.77 +/- 0.863	1.65 +/- 2.244	P=0.008[A] P=0.424[B]
Hit rate (HR)[D]	0.911 +/- 0.970	0.907 +/- 0.942	0.919 +/- 0.104	0.920 +/- 0.160	P=0.925[A] P=0.635[B]
False Alarm Rate (FR)[E]	0.006 +/- 0.009	0.019 +/- 0.326	0.006 +/- 0.007	0.0132 +/- 0.170	P= 0.008[A] P= 0.424[B]
Discriminability Index (Pr)[F]	0.905 +/- 0.99	0.889 +/- 0.968	0.913 +/- 0.105	0.906 +/- 0.162	P=0.499[A] P=0.565[B]
Bias (Br) [G,H]	-0.322 +/- 0.307	-0.274 +/- 0.244	-0.315 +/- 0.313	-0.230 +/- 0.263	P= 0.227[A] P=0.50[B]
Reaction Time	616.66 +/- 149.18	583.87+/- 129.79	566.94 +/- 102.417	541.24 +/- 114.965	P=0.016[A] P=0.049[B]

A= P value between OFF and ON tested by repeated measures two way ANOVA

B = P value between before surgery and after surgery tested by repeated two way measures ANOVA

C = Error of commission = Incorrect NoGo

D = Hit rate (HR) = Proportion of Go = Correct Go / Total number of Go

E = False alarm rate (FR) = Proportion of Incorrect NoGo = Incorrect NoGo / Total NoGo

F = Discriminability Index (Pr) = HR- FR

G = Bias (Br) = {FR/ (1-PR)}-0.5

H = No bias if Br = 0.5, Liberal Bias if Br<0.5, Conservative Bias if Br>0.5

A repeated measures two way ANOVA was performed with green house gassier correction which showed statistically significant effect of medication “OFF” and “ON” state on errors of commission / alarm time F(1,25)=8.25, p=0.00

No significant effect was noted of DBS surgery on errors of commission / alarm time and neither of any interaction between DBS and medication “ON” and “OFF” state.

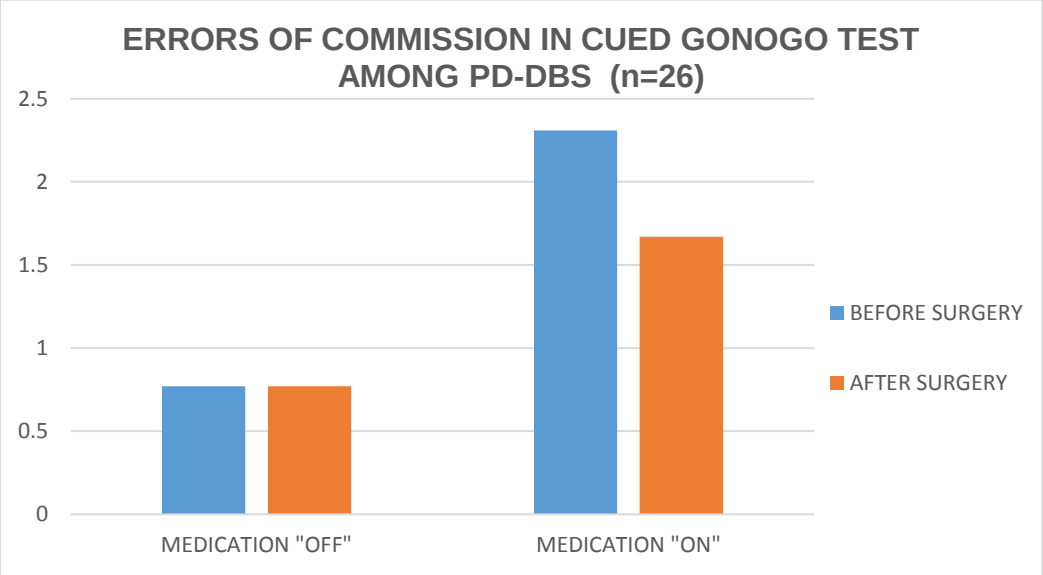

FIGURE 9 showing mean score for errors of commission in Cued GoNoGo test among PD-DBS subjects

A repeated measures two way ANOVA performed with green house gassier correction failed to reveal any statistically significant effect of either OFF and ON state or of DBS surgery on hit rate, discriminability index and bias as shown in table.

A repeated measures two way ANOVA showed statistically significant effect of OFF and ON state $F(1,25)=6.695$, $p=0.016$ as well as DBS surgery $F(1,25)=4.285$, $p=0.049$ on reaction time.

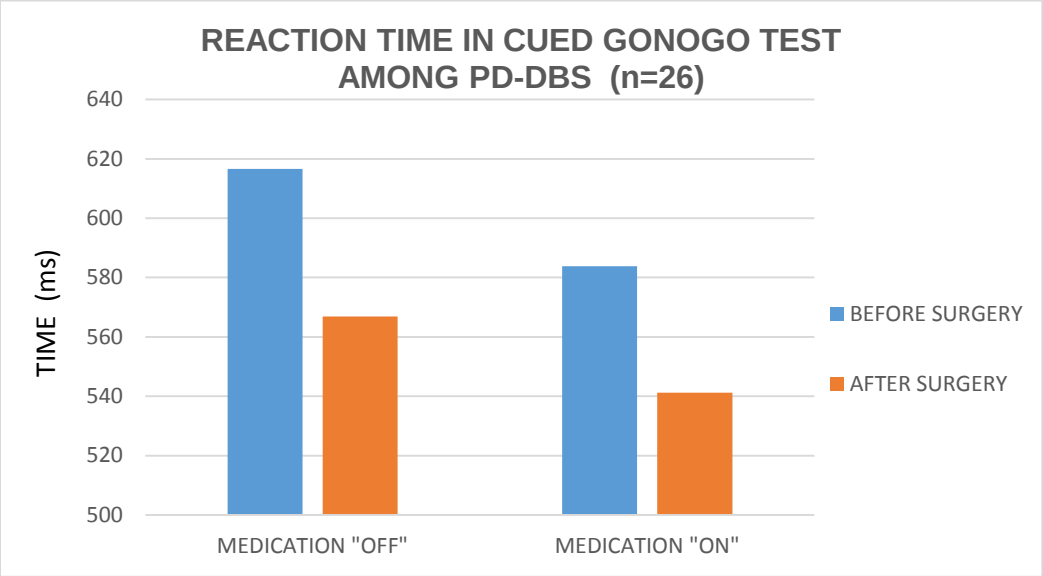

FIGURE 10 showing mean reaction time in Cued GoNoGo test among PD-DBS subjects

Iowa Gambling Task

A two way mixed and repeated measures ANOVA performed with green house gassier correction failed to reveal any statistically significant effect of surgery on PD-DBS group before and after surgery on medication "OFF"-stimulation "ON" IGT scores and neither did it show any difference in medication "OFF"-stimulation "ON" IGT scores among controls at two different visits, separated 3 months $F(1,53)=0.907$, $p=0.345$.

Similarly, medication "ON"-stimulation "ON" IGT score also failed to show any statistically significant difference on two way mixed and repeated measures ANOVA in PD-DBS group before and 3 months after surgery $F(1,53)=$,$p=$ and controls at 2 visits separated 3 months apart $F(1,53)=0.322$,$p=0.573$.

TABLE 4 showing total IGT scores among study group

Total IGT Score	PD-DBS (n=30)		PD-MEDICAL (n=25)		P value
	Before surgery	After Surgery (At 3 months)	Visit 1	Visit 2 (At 3 months)	
OFF IGT Score	0.47 +/- 13.92	0.67 +/- 9.83	0.12 +/- 12.90	-3.44 +/- 17.42	P=0.345[A]
ON IGT Score	-2.33 +/- 14.05	-1.20 +/- 12.16	-2.80 +/- 20.60	-3.92 +/- 21.15	P=0.573[A]

A= P value tested by 2x2 repeated measures ANOVA

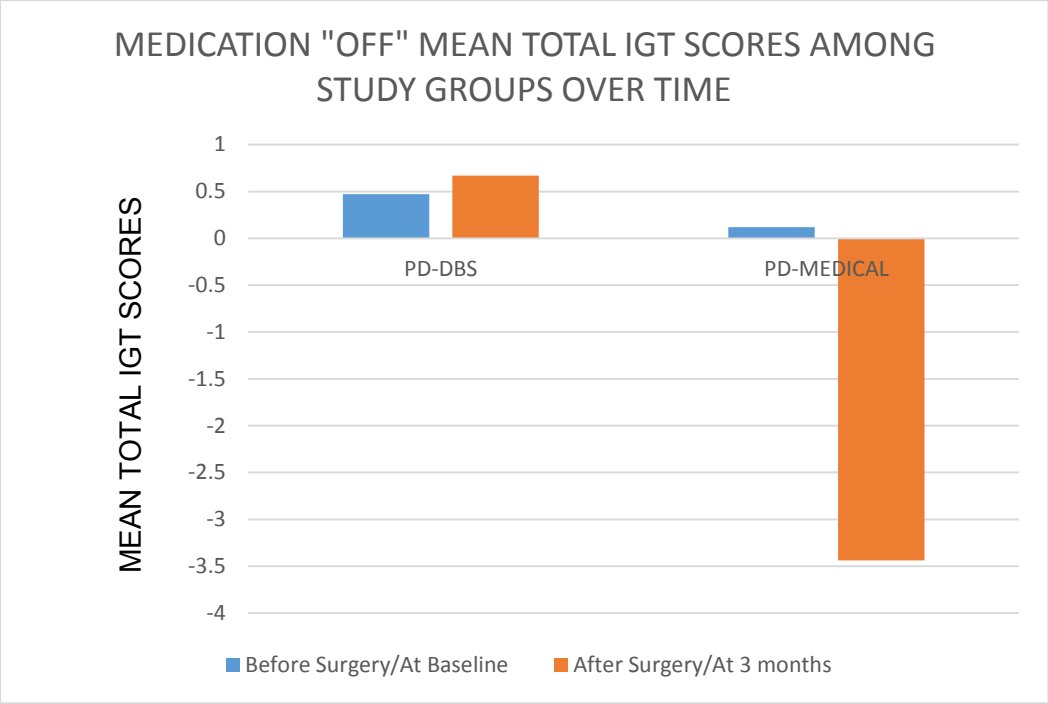

FIGURE 11 showing Medication "OFF" mean total IGT scores in study group over time

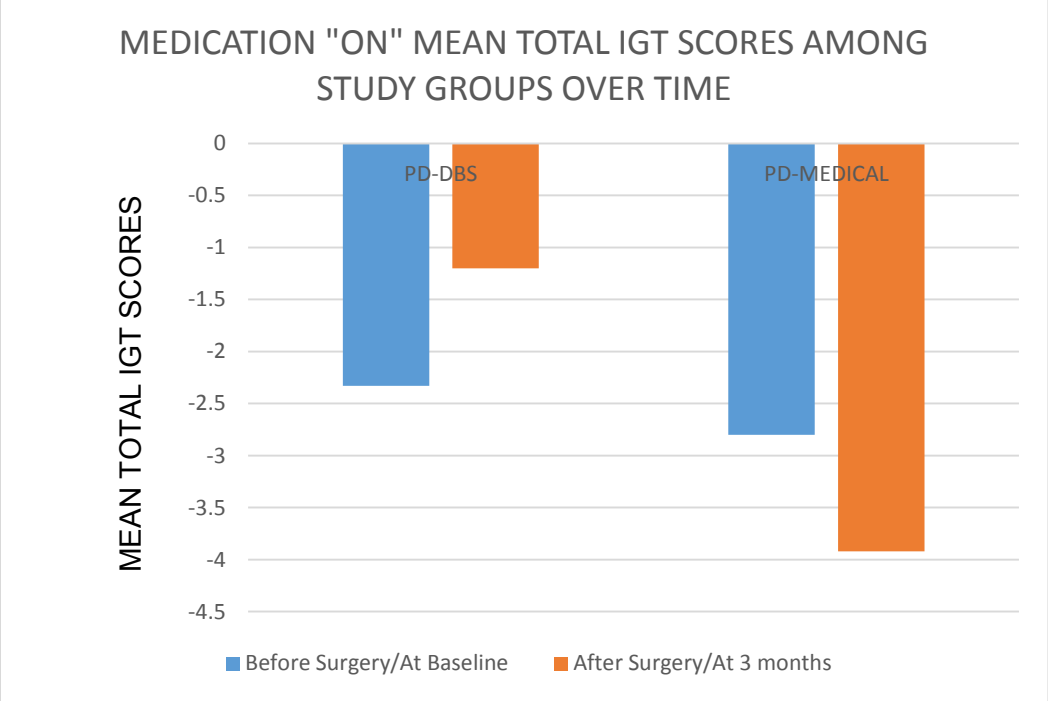

FIGURE 12 showing Medication "ON" mean total IGT scores in study group over time

IGT Block Scores

The differences between the number of cards chosen from the advantageous decks and the number of cards chosen from the disadvantageous decks for all conditions are shown in figure. The two way repeated measures analysis of variance (ANOVA) did not reveal any effect of following in medication "OFF" stimulatuion "ON" state

1) DBS surgery with study group [df(1,53), F=1.406,p=0.241]
2) study group with block scores [df(3.166), F=0.996,p=0.399]
3) DBS surgery with block scores [df(2.868), F=0.939,p=0.420

The two way repeated measures analysis of variance (ANOVA) did not show any interaction between block scores, surgery and study groups [df(2.868),F=1.040,p=0.387

The two way repeated measures analysis of variance (ANOVA) did not reveal any effect of following in medication "ON" stimulatuion "ON" state

1) DBS surgery with study group [df(1,53), F=0.036,p=0.850]
2) DBS surgery with block scores [df(3.351), F=1.624,p=0.180]

The two way repeated measures analysis of variance (ANOVA) did reveal significant effect of study group on block scores [df(3.515), F=2.892,p=0.029] in medication "ON" stimulatuion "ON" state

The two way repeated measures analysis of variance (ANOVA) did not show any interaction between block scores, surgery and study groups [df(3.351), F=1.622,p=0.180]

TABLE 5 MEAN MEDICATION “OFF” BLOCK IGT SCORES IN STUDY GROUPS

IGT BLOCK SCORES	PD-DBS BEFORE SURGERY	PD-DBS AFTER SURGERY	PD-MEDICAL BASELINE	PD-MEDICAL AFTER 3 MONTHS
BLOCK 1 (0-20)	-0.2	-1.07	0.96	-1.07
BLOCK 2 (21-40)	0.07	1.47	0.32	1.47
BLOCK 3(41-60)	0	-0.27	-0.48	-0.8
BLOCK 4 (61-80)	1.13	0.27	-0.64	-0.56
BLOCK 5 (81-100)	-0.6	0.8	0	-0.56

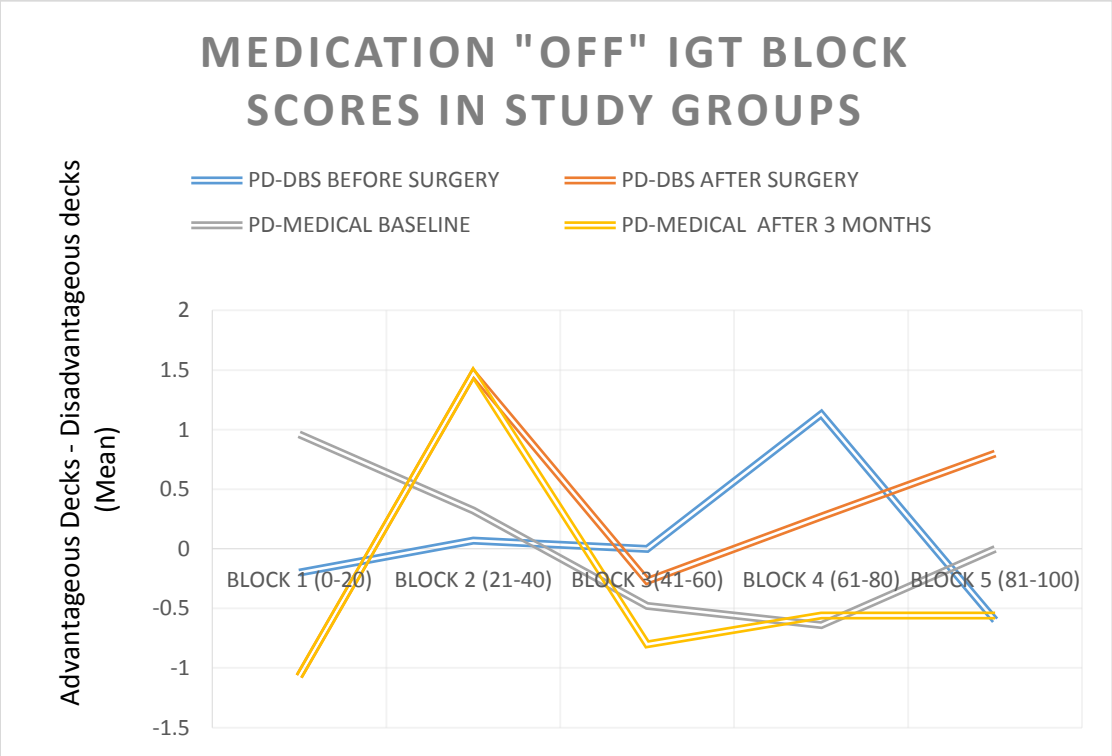

FIGURE 13 showing mean medication “OFF”-stimulation “ON” block IGT scores in study groups

TABLE6 MEAN MEDICATION “ON” BLOCK IGT SCORES IN STUDY GROUPS

IGT BLOCK SCORES	PD-DBS BEFORE SURGERY	PD-DBS AFTER SURGERY	PD-MEDICAL BASELINE	PD-MEDICAL AFTER 3 MONTHS
BLOCK 1 (0-20)	-1.4	-1.1	-0.2	-0.6
BLOCK 2 (21-40)	-2.1	0.5	0.2	0.2
BLOCK 3(41-60)	0.6	0.1	0	-0.2
BLOCK 4 (61-80)	0.6	0.2	-1.4	-2.1
BLOCK 5 (81-100)	0.8	-1.5	-1.5	-1.4

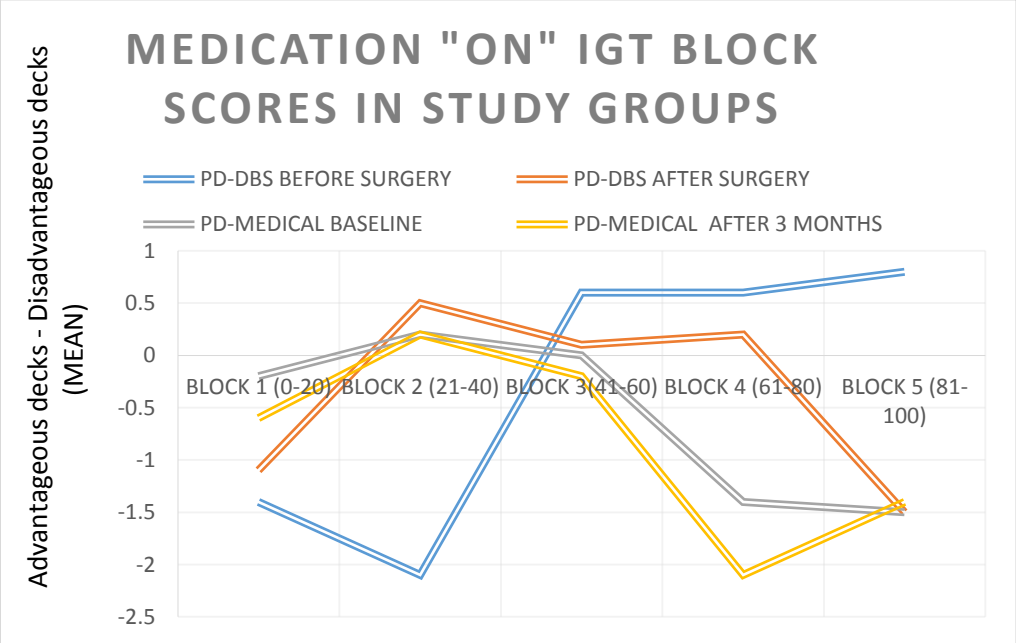

FIGURE 14 showing mean medication “OFF”-stimulation “ON” block IGT scores in study groups

DISCUSSION

The present study assessed the impact of STN-DBS and disease on response inhibition and impulsive decision making in advanced PD patients with an aim to resolve inconsistencies in previous research studies. Significant improvement in UPDRS scores was noted along with reduction in LEDD following STN-DBS surgery, reflective of the efficacy of STN-DBS. Self-assessment questionnaires assessing mood and affect i.e BDI and Apathy scales did not show any change before and after surgery. In fact, apathy which is considered to become worse after STN-DBS due to reduction in L-Dopa dose post-surgery did not worsen in our subjects based on Apathy scores. There was an improvement in the impulse control related behavior as reflected by mMIDI scale. Only 1 out of 5 were positive on mMIDI after STN-DBS surgery. However, BIS-11 scores did not reveal any significant change in the scores in PD-DBS group before and after surgery.

In the present study, there was no difference in the IGT total scores before and after STN-DBS when tested in the medication-OFF state. This suggests lack of direct effect of STN DBS on impulsivity or impaired decision making. On closer look at the graphs, there was a trend towards improvement in total IGT scores after STN DBS in PD-DBS group as compared to PD-Medical group who did not undergo surgery, though it did not reach statistical significance. A larger sample size may be required to rule out a true difference, though ours is the study with one of the highest number of subjects. Considering the possibility of STN-DBS modulating impulsivity only in the setting of dopaminergic therapy, we also compared the IGT scores before and after surgery in the medication-ON state, which revealed a similar lack of effect of STN-DBS. The IGT block scores were also similar before and after surgery in PD DBS group consistent with lack of effect of STN DBS on impaired decision making. Taking

note of Cued GoNoGo results, our study failed to demonstrate any effect (positive or negative) of STN DBS before or after surgery on Cued GoNoGo testing.

STN is a small lens shaped nucleus, which forms the part of the indirect and hyperdirect basal ganglia pathways. It is topographically organized, having functional subdivisions i.e sensorimotor, associative and limbic sectors[46,51]. Frank et al[44] postulated, based on neurocomputational models that STN sends a global NoGo signal via indirect / hyperdirect pathways, leading to transient thalamocortical inhibition giving extra time for information processing so as to deliberate appropriate responses. In therapeutic neurostimulation for PD, the dorsal sensorimotor sub-territory of STN is stimulated, leading to improvement in motor symptoms of PD. It has been postulated that it is either direct ventral STN DBS stimulation or spread of current to limbic territories which causes cortico-limbic circuit effects[46,51]. This notion is supported by studies[46,51,54,55] which have shown the effect of stimulation parameters such as current spread and electrode position on cognitive tasks.

Our study failed to show any such cognitive effect of DBS on IGT and Cued GNG tests, which may be explained by accuracy of electrode placement and stimulation parameter settings essentially stimulating dorsal STN DBS with minimal spread across cortico-limbic structures, however we don't have the MRI studies demonstrating lead position to substantiate the explanation. Alternatively, another hypothesis could be that STN DBS did increase impulsivity but LEDD reduction after surgery negated any increase in impulsivity due to STN DBS. This is supported by the finding that LEDD reduced by ~40% after STN DBS, in cases group in our study. This alternative hypothesis is less plausible upon comparing medication OFF vs medication ON IGT scores, in both PD-DBS and PD-Medical group in our study, which showed no statistically significant change. In fact, similar results were noted in previous studies comparing premedication OFF vs ON state that found no change. Comparing medication ON

vs 12 hours OFF medication may not reveal the true effect of L-Dopa on IGT scores as the cognitive effects may not be responsive to short duration medication withdrawal of 12 hours.

The results of our study were comparable with those of Czernecki et al[47] and Genko Oyama et al[49] which also showed that total IGT scores did not differ in PD patients after STN DBS. The study by Czernecki et al[47] also did not show any worsening of apathy which was in accordance with the results of our study. However, there's was a case control study and ours is a cohort study giving more strength to our results. The main difference in the Oyama et al[49] study as compared to ours was that the IGT scores were measured 4-6 weeks post STN DBS surgery in medication ON stimulation OFF and stimulation ON states. So the acute lesioning effects of STN-DBS could be a factor. Also they noted that DBS patients performed worse in last block of the task when compared with controls suggesting a possible increase in impulsivity due to DBS which was contrary to our results.

Sharp differences were noted when we compared our results with that of Castriole et al[50]. In this study by Castriole et al[50], IGT scores improved significantly post DBS irrespective of stimulation OFF or ON state comparable to their healthy controls. These differences can be explained by striking differences in the baseline characteristics between out study group as compared to theirs. Firstly, 8 out of their 20 DBS subjects had active hyperdopaminergic behaviours (ICD) as compared to our study in whom none of the patient had any active ICD. LEDD was higher in their group (Mean = 1459mg) as compared to our group (Mean = 1012mg). LEDD reduced by ~74% in their study as compared to ~40% in our study. Dose of dopamine agonist was not kept constant in their study which was reduced from mean of 458mg to mean 158mg after STN DBS. Active ICD and variable dopamine agonist dose before and after surgery could have been the possible confounders in their study. In comparison, our results suggest that STN-DBS alone is unlikely to improve or worsen impulsivity in advanced

PD and any observed effects may be due to reduction of concomitant medications and subsequent resolution of clinical ICD.

The study by Evens et al, a case control study comparing PD-DBS, PD-nonDBS and healthy controls, noted a significant decrease in total IGT scores in PD-DBS group as compared to PD-nonDBS group. However, in their study, major differences were noted in the duration of PD as well as Hoehn and Yahr stage among PD-DBS group when compared with PD-nonDBS group. Mean duration of PD in PD-DBS group was 15.2 years as compared to 7.3 years in PD-nonDBS. Mean Hoehn and Yahr staging was 3.17 in PD-DBS vs 2.3 in PD-nonDBS group. In our study, no such difference was noted between study groups.

IGT measures decision making in ambiguous situation as one uses the feedback gained through-out the test to identify strategies that maximize the initial bet so as to perform successfully[18]. Anatomical correlate for IGT performance is originally considered to be ventromedial prefrontal cortex[18,19]. But various PET and functional neuroimaging studies have found deficits in limbic, orbitofrontal cortex and ventral striatal, the so called limbic loop circuit in PD without dementia with poor performances on IGT[19,27]. But that having said, the integrity of prefrontal cortex is a prerequisite for successful performance of IGT. Physiologically this behavior is attributed to excess DA levels in striatum[44]. Clinical studies have identified dopamine agonists to be associated with higher risk of impulsivity, mediated through their D3 receptor affinity. It has been demonstrated in various studies[18,19] that normal healthy individuals learn to progressively select advantageous decks as they complete the IGT task as reflected upon by block wise improvement in subset IGT scores over 100 cards play. Our study showed that both cases who underwent DBS and control PD patients failed to show any improvement in 20 block each subset scores, thus reflecting failure of advanced PD patients to adapt and learn from mistakes, having a myopic vision for future, preferring short term gains over long term losses which was consistent with the previous studies[25-35]. Failure of IGT scores

to show any change across both study groups in our study suggest dysfunction of the orbitofrontal cortex, amygdala and limbic circuit loop either due to hyperdopaminergic activity or due to neurodegeneration in advanced PD. All the cases were screened with addenbrooke's cognitive examination and none of them had any clinically significant executive dysfunction suggesting that the dorsolateral prefrontal is unlikely to be implicated for poor performances in our subjects.

Various other studies have measured deficits in a cognitive tasks using GoNoGo testing[43,45,46], stroop test[66], stop signal tasks[66] requiring either response selection under conflict or inhibiting prepotent response. Results from all these studies were conflicting with some showing worsening, some improvement and some no effect of DBS on impulsivity. Variation in the nature of the task, the number of patients in the previous studies, precise active contact position in the STN DBS are all likely to account for some of the differences across studies. Our study did note an increase in errors of commissions between medication OFF and ON state in cases before and after DBS suggesting that dopaminergic therapy increases motor impulsivity in advanced PD which was in accordance with the results of metanalysis by Manza P et al[37] which noted that performances in tasks in PD varied with duration of PD. According to Manza et al[37], dopaminergic drugs tended to improve performances in early PD but worsen in advanced PD.

Strenghts of the study

Our study was different from the previous studies, mainly in control and measurement of confounders that can potentially affect the performance in the neuropsychological tests. Firstly, none of the active ICD patients were included in the study. Second, the dose of dopamine agonist which is a major determinant of impulsivity was kept constant before and after surgery so as to measure true effect of DBS. Thirdly, mood and motivational drive can

significantly affect the task performance. So patient with overt depression were excluded from the study. Apathy, reduced motivation and depression which is known to follow DBS was measured via self-assessment questionnaire methods and no statistically significant difference was noted in the mean value of Apathy scores or BDI scores suggesting mood is unlikely to be a significant confounder in the study. Fourthly, controls were assessed 4 times, twice at visit 1 and twice after 3 months in medication ON and OFF state to essentially assess whether there is any effect of learning on repeatedly doing the same task. Our study failed to show any such learning effect which was consistent with previous studies. Finally, cases were tested 3 months after surgery to negate the potential contribution from lesioning effects of DBS.

Limitations of the study

The limitations of our study are that we did not test PD-DBS subjects after surgery in medication "OFF" stimulation "OFF" as was done in all other previous studies due to practical constraints. Second, the exact subdivision of the STN stimulated in the subjects, whether dorsal vs ventral was not assessed. So further studies will be needed in that direction analyzing neuroimaging, the contact positions being stimulated and current amplitude and then correlating it with tests of impulsivity.

CONCLUSION

1) Bilateral STN-DBS markedly improves the motor symptoms of Parkinson's disease as evidenced by reduction in L-Dopa dosage and improvement in UPDRS scores.
2) Bilateral STN-DBS failed to show any change in response inhibition or impulsive decision making in advanced PD patients.
3) Reduction in impulsive behavior as evidenced by pre and post mMIDI scores which could also be attributable to L-dopa reduction after surgery.
4) Dopaminergic medication likely contributes to the impairment in response inhibition tasks.
5) Advanced PD leads to impaired ability of patients to learn from negative decision outcomes independent of dopaminergic medication status.

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ANNEXURE

LIST OF ABBREVIATIONS

1) PD - Parkinson’s Disease
2) BIS-11 - Barratts Impulsivity Scale -11
3) GNG – GoNoGo
4) IGT – Iowa Gambling Task
5) LEDD – Levo-Dopa Equivalent Daily Dose
6) STN-DBS- Subthalamic Nucleus - Deep Brain Stimulation
7) ICD - Impulse Control Disorder
8) MMSE - Mini Mental State Examination
9) BDI - Becks depression inventory
10) mMIDI - modified Minnesota Impulsive Disorders Interview
11) UPDRS - Unified Parkinson's Disease Rating Scale
12) ANOVA - Analysis of variance
13) HR = Hit rate
14) FR = False alarm rate
15) Pr = Discriminability Index
16) Br = Bias
17) AD = Advantageous Decks
18) DD = Disadvantageous Decks

PROFORMA

NAME: AGE/GENDER: HOSP. NO:

ADDRESS: PHONE NO:

GROUP: PD-DBS/ PD-CONTROL

AGE OF ONSET: DURATION OF ILLNESS:

Ever had ICD: Y/N Active ICD: Y/N

Drug History

Drug (Name)	Duration (yrs)	Pre DBS daily dose	Post DBS daily dose	Pre DBS LEDD (mg)	Post DBS LEDD (mg)	% reduction in LEDD
L-dopa						
Pramipexole						
Ropinirole						
Amantadine						
Entacapone						
Rasagiline						
Selegiline						
Trihexyphenidyl						
Total LEDD (mg)						

Pre DBS Evaluation

UPDRS III (on): UPDRS III (off): H&Y (on): H&Y (off):

MMSE: /30 ACE: /100 Cognitive impairment: Y/N

HADS-A: /21 HADS-D: /21 BDI: /63 Depression: Y/N

Apathy Scale: /42 Apathy (>14): Y/N

Barratt Impuslvity Scale: Impulsive (>72): Y/N

mMIDI ICD: Y/N

BD: Y/N CG: Y/N CSB: Y/N CE: Y/N PB: Y/N

Post DBS Evaluation (3 months)

Apathy Scale: /42 Apathy (>14): Y/N

Barratt Impuslvity Scale: Impulsive (>72): Y/N

mMIDI ICD: Y/N

BD: Y/N CG: Y/N CSB: Y/N CE: Y/N PB: Y/N

DBS parameters

STN Right: Contact: Voltage_____V Frequency_____Hz PW_____μS

STN Left: Contact: Voltage_____V Frequency_____Hz PW_____μS

Proforma Completed by: _____ _____

Signature Name

Date:

IGT SCORE SHEET

Name: **Hospital Number:** **Study:**

Condition: **Date:**

Advantageous Decks (AD): 1 2 3 4 Disadvantageous Decks (DD): 1 2 3 4

Number of Advantageous Decks: Number of Disadvantageous Decks:

IGT Total Score (number of AD-number of DD):

IGT Mean Latency: _____ms

IGT Advantageous Latency: _____ms

IGT Disadvantageous Latency:_____ms

IGT Series Score:

Block	Block1	Block2	Block3	Block4	Block5
AD					
DD					
Score (AD-DD)					
Mean Latency(ms)					
AD Latency (ms)					
DD Latency (ms)					

GO NO GO SCORE SHEET

Name: **Hosp Number:** **Study:**

Condition: **Date:**

Total Go: Correct go: Proportion of Go (Hit rate, HR):

Incorrect Go (Error of omission):

Total NoGo: Correct NoGo: Proportion of correct NoGo:

Incorrect NoGo (Error of commission):

Proportion of Incorrect NoGo (False alarm rate, FR):

Reaction time for Go:

Reaction time for NoGo (False Alarm):

Discriminability Index (Pr): HR- FR=

Bias (Br): {FR/ (1-PR)}-0.5=

No bias (Br=0.5)/ Liberal Bias (Br<0.5)/ Conservative Bias (Br>0.5)

Investigator: _____ **Date:_____**

BIS-11

1.I ‘squirm’ at plays or lectures

Not at all-1	Slightly-2	Some-3	A lot-4

2.I am restless at the theater or lectures

Not at all-1	Slightly-2	Some-3	A lot-4

3.I don’t pay attention

Not at all-1	Slightly-2	Some-3	A lot-4

4.I concentrate easily

Mostly-4	Some-3	Slightly-2	Not at all-1

5.I am a steady thinker

Mostly-4	Some-3	Slightly-2	Not at all-1

6.I act ‘on impulse’

Not at all-1	Slightly-2	Some-3	A lot-4

7.I act on the spur of the movement

Not at all-1	Slightly-2	Some-3	A lot-4

8.I buy things on imulse

Not at all-1	Slightly-2	Some-3	A lot-4

9.I make up my mind quickly

Not at all-1	Slightly-2	Some-3	A lot-4

10.I do things without thinking

Not at all-1	Slightly-2	Some-3	A lot-4

11.I spend or charge more than I earn

Not at all-1	Slightly-2	Some-3	A lot-4

12.I am happy go lucky

Not at all-1	Slightly-2	Some-3	A lot-4

13.I am a careful thinker

Mostly-4	Some-3	Slightly-2	Not at all-1

14.I plan tasks carefully

Mostly-4	Some-3	Slightly-2	Not at all-1

15.I am self controlled

Mostly-4	Some-3	Slightly-2	Not at all-1

16.I paln trips well ahead of time

Mostly-4	Some-3	Slightly-2	Not at all-1

17.I plan for job security

A lot-4	Some-3	Slightly-2	Not at all-1

18.I say things without thinking

Not at all-1	Slightly-2	Some-3	A lot-4

19.I like to think about complex problems

A lot-4	Some-3	Slightly-2	Not at all-1

20.I like puzzles

A lot-4	Some-3	Slightly-2	Not at all-1

21.I save regularly

Mostly-4	Some-3	Slightly-2	Not at all-1

22.I am more interested in the present than the future

Not at all-1	Slightly-2	Some-3	A lot-4

23.I get easily bored when solving thought problems

Not at all-1	Slightly-2	Some-3	A lot-4

24.I change residences

Not at all-1	Slightly-2	Some-3	A lot-4

25.I change jobs

Not at all-1	Slightly-2	Some-3	A lot-4

26.I am future oriented

A lot-4	Some-3	Slightly-2	Not at all-1

27.I can only think about one problem at a time

Not at all-1	Slightly-2	Some-3	Mostly-4

28.I often have extraneous thoughts when thinking

Not at all-1	Slightly-2	Some-3	A lot-4

29.I have racing thoughts

Not at all-1	Slightly-2	Some-3	A lot-4

30. I change hobbies

Not at all-1	Slightly-2	Some-3	A lot-4

CONSENT FORM

Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram, Kerala-695011

TITLE OF STUDY: **"Effect of Subthalamic Nucleus-Deep Brain Stimulation surgery on impulsivity in Parkinson's Disease patients"**

Principal Investigator: Dr. Syam Krishnan

This is an important form. Please read it carefully. It tells you what you need to know about this study. If you agree to take part in this research study, you need to sign this form. Your signature means that you have been told about study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why is this study being done?

We have identified that upto 31% of patients suffering from Parkinson's disease develop a problem called impulse control disorder (ICD) during their treatment. This condition is characterized by an inability to control an impulse and to stop performing an act that is harmful to the person or others. Treatment with dopamine agonist drugs such as Pramipexole, Ropinirole is a risk factor for developing ICD. Increased impulsivity is thought to underlie development of ICD. Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) surgery is done to control the motor symptoms of Parkinson's disease. This study plans to examine whether impulsivity will improve after STN-DBS surgery in Parkinson's disease by comparing patients who undergo STN-DBS surgery with those who are only treated with medications. Impulsivity is tested using 2 simple computerized tasks.

You may participate in this study if you have Parkinson's disease and are selected to undergo DBS surgery at the Comprehensive Care Center for Movement Disorders at SCTIMST or you are a suitable candidate for deep brain stimulation but you have chosen not to undergo it or have medical conditions that do not allow surgery to be performed on you

How many people will take part in the study?

The plan is to include 25 patients with PD who will undergo DBS surgery and 25 PD patients who are only medically treated.

What will happen in the study?

Your participation will require:

- You will be interviewed by your doctor and a neuropsychologist who will provide you a set of questions to be answered and instruct you to complete two computer based tasks that assess impulsive choices during decision making.
- First task requires you to choose cards one by one, for each card drawn a particular reward or penalty will be displayed and you have to try to maximise your rewards while minimising losses.
- The second task requires you to press a button when shown a colored shape.

- These tests will be performed twice before DBS surgery (with medication and without medications overnight, procedures that are routine in the pre surgical assessment) and twice 3 months after DBS. PD patients who are not undergoing DBS surgery (controls) will be also be tested twice three months apart, both in medication 'ON' condition.
- You will also be asked to provide clinical details including age, gender, duration of illness, age of onset of PD, duration of dopamine replacement therapy and current medication.
- As part of routine pre-surgery evaluation for DBS, you will also undergo assessment of motor functions, mental abilities, memory and mood and this data will be used in this study.

How long will I be in the study?

You will be in the study for a minimum of 3 months as tests will be repeated after 3 months.

Will any biological sample(s) be stored and used in the future?

This study does not involve donation or storage of any biological samples.

What are the risks of the study?

This study does not involve any blood draw/ other specific tests/ administering of drugs specifically for the study. During the course of this study, psychiatric or impulse control symptoms may be identified, in which case your doctor will initiate treatment accordingly, if required. Your privacy is very important to us and the results of the tests performed on you will be treated as highly confidential. Such information will not be revealed to you unless it suggests a treatable disease.

Are there benefits to taking part in this study?

You will receive no direct benefit from participation in this study.

What other choices do I have if I don't take part in this study?

The study is only being done to gather scientific information. You may choose not to take part in this study.

What are the costs of the tests and the procedures?

You will not need to pay for any tests or procedures, which are done just as a part of the research study.

Who can answer my questions?

You may talk to Dr. Syam Krishnan at any time about any question you have on this study. You may contact Dr. Syam Krishnan calling his office in SCTIMST at the phone number: 0471 - 2524481. If you have any other concerns you can call the ethics committee secretary Dr. Mala Ramanath at the following number: 0471-2524234.

Will I lose my rights if I do not take part in this study?

Taking part in this research study is your decision. You do not have to take part in this study if you are unwilling. Also you will be at the liberty to withdraw at any stage of the study in case you want to withdraw. Your medical care SCTIMST now or in the future will not be affected whether or not you take part in this study or withdraw at any stage of the study. You will be told of important new findings that may happen, if you choose to have that information. You do not give up any of your rights by taking part in this study.

What about confidentiality?

Data from this study may be published. However, your name and other identifying information will not be sent outside of SCTIMST.
I had an opportunity to have my questions answered. I have been given a copy of this form. I agree to take part in this study.

_____	_____	_____
(Date)	(Signed and printed name of Participant)	(Clinic number)

_____	_____
(Date)	(Signed and printed name of Individual obtaining consent)

DECLARATION BY THE SUBJECT

I have read the informed consent form. I agree to use the data derived from the study for scientific purposes (like scientific publications in Medical Journals/ presentation in scientific forums etc) without any restriction. After understanding the aims of the study, my role in the study and my right to refuse participation without facing any consequences and clarifying my doubts, I voluntarily agree to participate in the study.

Signature

Name of the subject:

Address:

Place
Date

DECLARATION BY THE PRINCIPAL INVESTIGATOR

I have explained regarding the study to the study participant who has signed the informed consent form (ICF) above. The consent was given and the ICF was signed voluntarily by the participant. A copy of the signed consent form is given to the participant.

Place:
Date: Principal Investigator

Plagiarism Checker X Originality Report

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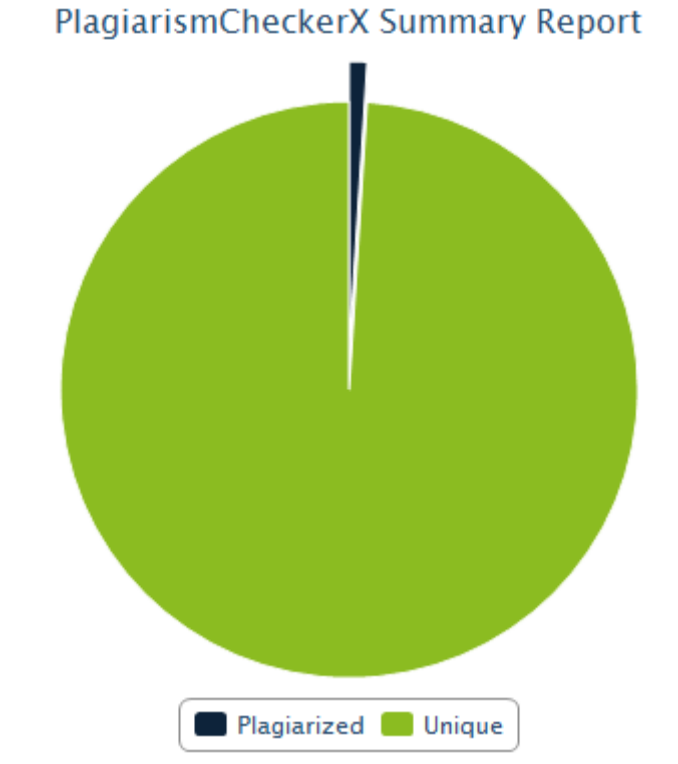

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011, INDIA
(An Institute of National importance under Govt. of India)

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/770/JUNE-2015

26-06-2015

Dr. Syam. K
Associate Professor
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Syam,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "EFFECT OF SUBTHALAMIC NUCLEUS-DEEP BRAIN STIMULATION SURGERY ON IMPULSIVITY IN PARKINSON'S DISEASE PATIENTS (IEC/770)" on 12th June, 2015.

The following documents were reviewed:

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 21.05.2015.
2. IEC Application form.
3. TAC Approval Letter.
4. TAC Application form.
5. Investigator's response to questions/suggestions from TAC.
6. Study proposal.
7. Informed consent forms in English and Malayalam.
8. Proforma.
9. Iowa Gambling Task (IGT) Score sheet.
10. "Go-on-go" score sheet..
11. Short CVs of PI and Co-PI's.

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The following members of the Ethics Committee were present at the meeting held on 12th June, 2015 at G. Parthasarathi Board Room, AMCHSS, SCTIMST.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Justice Gopinathan. P.S	BSc. LLB	Male	Legal Expert (Chairperson)	No
2.	Dr. J. M. Tharakan	MD	Male	Clinician (Cardiologist)	Yes
3.	Shri. O.S. Neelakandan Nair	BE	Male	Engineer	Yes
4.	Dr. R V G Menon	PhD	Male	Lay Person	No
5.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro-Enterologist)	No
6.	Dr. Rema M. N	MD	Female	Pharmacologist	No
7.	Smt. Sathi Nair	MA	Female	Lay Person	No
8.	Dr. Kala Kesavan. P	MD	Female	Pharmacologist	No
9.	Dr. K R S Krishnan	ME, PhD	Male	Biomedical Scientist/Engineer	No
10.	Dr. K. Jayakumar	MS, MCh	Male	Clinician (Surgeon)	Yes
11.	Dr. Mala Ramanathan	MSc, PhD, MA	Female	Ethicist/Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC