

Impulse control disorders following subthalamic nucleus deep brain stimulation in Parkinson's disease: A retrospective analysis

Theresa Mallia, Norma McKean, Josanne Aquilina

Background

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is considered in patients with Parkinson's disease (PD) when there is suboptimal control of motor symptoms. While effective at improving some of these symptoms, its effect on impulsive behaviour can be variable. This retrospective analysis examines the incidence of post-operative impulse control disorders (ICDs) in PD patients who underwent bilateral STN-DBS surgery between January 2011 and December 2018.

Materials and Methods

A questionnaire based on the DSM-5 criteria was used for data collection.

Results

The patient cohort involved a total of 38 patients. Questionnaires were returned by 36 patients (95%). Seven patients (19%) fulfilled diagnostic criteria for ICDs, while six patients (17%) showed features of ICDs that did not fulfill diagnostic criteria.

Conclusion

A significant proportion of our patient cohort reported impulsive behaviour following STN-DBS surgery. This finding therefore warrants evaluation during the follow-up visits of such patients.

Dr Theresa Mallia Elull,
MD, MRCP (UK)
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

Dr Norma McKean
MD, MRCP (UK), FEBN
Department of Neurosciences,
Mater Dei Hospital,
Msida, Malta

Dr Josanne Aquilina
MD, FRCP(Lond), FRCP(Edin)
Department of Neurosciences,
Mater Dei Hospital,
Msida, Malta

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a recognised treatment modality in the management of Parkinson's disease (PD). The mechanism of action, although not yet fully understood, involves selective modulation of disrupted basal ganglia thalamocortical circuits and basal ganglia-brainstem projections, allowing closer to normal motor and non-motor network function.¹

The primary indication for STN-DBS surgery in PD is disabling motor fluctuations and/or dyskinesias despite optimal medical therapy. Long-term results have confirmed substantial clinical improvement in medically refractory tremor, dopaminergic-responsive motor and non-motor features, as well as in the quality of life of these patients.²⁻⁴

The effect of STN-DBS on impulsive behaviour and behavioural addictions can be variable. In patients with PD, this behaviour has been linked to dopaminergic treatment, especially dopaminergic agonists with selective affinity for D2-D3 dopamine receptors. Several prospective studies have shown either no increase or alleviation of impulsive behaviour following this procedure. However, worsening of pre-existing behavioural disorders and onset of new impulse control disorders (ICDs) have also been recorded.⁵ The four main types of ICDs encountered are pathological gambling, compulsive buying, hypersexuality and compulsive eating.⁶

Risk factors for the development of ICDs include male gender, young age or younger age at PD onset, a past history of smoking, substance misuse, depression and a personality profile characterised by impulsiveness.^{6,7} Cultural factors may also contribute to both the prevalence and type of ICD depicted by the patient.^{8,9}

This retrospective analysis examines the number of patients who developed impulsive behaviour following STN-DBS surgery. It was performed as part of a service evaluation and continued patient follow-up.

MATERIALS AND METHODS

All PD patients who underwent bilateral STN-DBS surgery between January 2011 and December 2018 in Mater Dei Hospital, Malta, were recruited in this analysis. All patients were above 18 years of age and consented to participation. These patients had shown significant improvement with levodopa therapy, but despite optimal treatment, symptoms were uncontrolled as the disease progressed. None of the patients had a significant history of psychiatric disorders or dementia.

A questionnaire based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) was created in both English and Maltese and answered by the patient cohort. The drug history and date of DBS surgery were also registered. All participants were taking at least one anti-parkinsonian drug, and the use of carbidopa, levodopa, entacapone, rasagiline, benserazide and ropinirole, either alone or in combination, was recorded.

To compare clinical features between groups, continuous data was expressed as mean $\pm$ standard deviation (SD), whilst differences in continuous variables were examined using the paired t-tests.

RESULTS

The analysis was carried out on 36 eligible participants, 24 male and 12 female. The mean age at surgery was 58.7 years (SD $\pm$ 9.6), with the mean follow up after surgery being 51.2 months (SD $\pm$ 28.2).

Of the 35 patients who answered the questionnaire in its entirety, seven patients (19%) fulfilled diagnostic criteria for ICDs, with two of these having two concomitant ICDs. Features of ICDs not reaching diagnostic criteria was documented in 10 patients (29%), with four of these patients having another ICD. Therefore, 13 patients (36%) had either a confirmed diagnosis, or features of, ICDs. One male participant declined to answer questions related to hypersexuality, however he denied other post-operative impulsive behaviour.

Of the seven patients who were found to be suffering from ICDs, five (71%) were male. The two participants who developed two concomitant ICDs were both male. Three males and three female patients developed features of ICDs but did not fulfil diagnostic criteria. Of the remaining 23 patients with no features of ICDs, 19 (83%) were male and 8 (17%) were female.

Seven (54%) of the 13 patients with impulsive behaviour were on dopamine agonists (ropinirole), while ten (43%) of the 23 patients without features of ICDs were on ropinirole treatment. Furthermore, eight (35%) of the 23 patients without ICDs were on a single anti-parkinsonian medication, while three (43%) of the seven patients with ICDs and one (17%) of the six patients with ICD features were on a single drug. When calculating the dopamine equivalent doses between the patients who developed impulsive behaviour and those who did not, no significant difference was established ($p=0.21$).

When analysing the difference between the patients with features of impulsivity and those without, there was no statistically significant difference in age at time of study ($p=0.4$), age at DBS insertion ($p=0.2$), and time from DBS surgery to analysis ($p=0.9$).

Interestingly, one patient with a history of non-pathological gambling prior to PD diagnosis developed hypersexuality and compulsive eating post-operatively; but did not develop pathological gambling.

A graphical breakdown of separate ICDs can be found below in [Figure 1](#), [Figure 2](#) and [Figure 3](#) and a more detailed account of the results in [Table 1](#).

DISCUSSION

This analysis confirms that ICDs (19%) and features of ICDs (17%) are evident after chronic STN-DBS (with a mean follow-up of 51.2 months).

Several studies have been performed to assess the development of impulsive behaviour following STN-DBS insertion. A retrospective analysis by Merola et al including 150 participants with a post-operative follow up period of 51.6 months ($SD \pm 25.2$), showed that 7.3% of post-operative STN-DBS patients developed new-onset ICDs, with these being more common in females. Furthermore, 45% of the patients suffering from the impulsive behaviour were noted to have developed multiple ICDs, namely pathological gambling, hypersexuality and/or compulsive shopping.¹¹

Two other retrospective studies also showed the occurrence of de-novo impulsive behaviour following bilateral STN-DBS surgery. Kim et al showed that nine of 89 patients (8%) developed such behaviours, with these being more common in males.¹² 19% of the population studied by Halbig et al developed ICDs after an average of 34 months following the surgery, with the most common being compulsive shopping.¹³

A prospective analysis by Amami et al reported that 6 out of 43 patients (14%) developed de-novo impulse control behaviours after 36 months of continuous STN-DBS. However, these symptoms were transient and lasted for an average of 15 months. Compulsive eating was the most ICD reported, whilst pathological gambling was the least.¹⁴

Similar to our results, a male predominance¹²⁻¹⁴ and absence of a relationship between impulsivity and post-operative dopaminergic doses is reported in the above studies.^{12,14} The analysis by Amami et al¹⁴, highlights the importance of prospective studies, as such symptoms may be transient and resolve spontaneously.

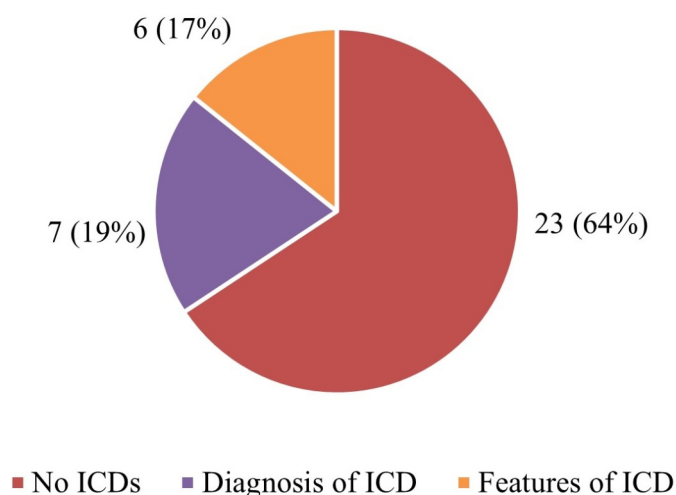


Figure 1 Post-operative STN-DBS patients

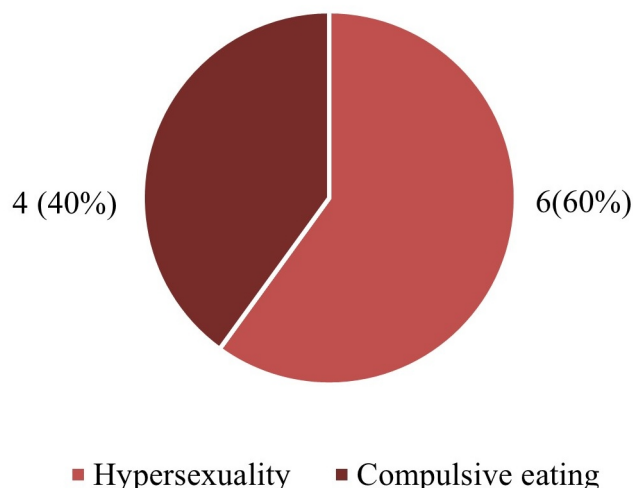


Figure 2 Features of ICDs not fulfilling diagnostic criteria

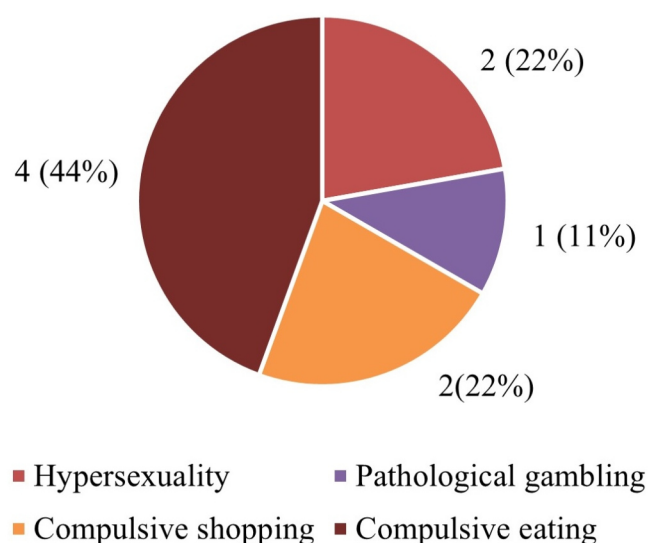


Figure 3 ICDs reaching diagnostic criteria

Table 1 Patients with post-operative impulsive behaviour

Patient	Age*, Gender	Year of DBS surgery	Post-op ICDs/ features of ICDs	Anti-parkinsonian medication	Dopa equivalent dose of ropinirole ¹⁰
1	57, male	2011	Compulsive shopping Features of hypersexuality	Ropinirole 2mg TDS	120mg
2	57, female	2012	Features of compulsive eating	Stalevo® (entacapone- levodopa- carbidopa) Ropinirole 8mg TDS	480mg
3	70, male	2013	Pathological gambling Hypersexuality Features of compulsive eating	Stalevo® Ropinirole 2mg TDS	120mg
4	77, female	2013	Features of compulsive eating	Stalevo® Ropinirole 3mg TDS Amantadine	180mg
5	70, female	2014	Features of hypersexuality	Stalevo® Ropinirole 1mg TDS	60mg
6	74, female	2015	Compulsive eating Features of hypersexuality	Sinemet® (carbidopa- levodopa) Ropinirole 3.5mg TDS	210mg
7	57, male	2015	Features of hypersexuality	Stalevo® Sinemet®	/
8	70, male	2016	Compulsive shopping Hypersexuality	Madopar® (levodopa- benserazide) Carbidopa	/
9	67, male	2016	Features of compulsive eating	Ropinirole 2mg TDS Rasagiline	120mg
10	62, male	2017	Compulsive eating	Stalevo®	/
11	52, female	2017	Compulsive eating	Co- careldopa® (carbidopa- levodopa)	/
12	47, male	2017	Features of hypersexuality	Stalevo®	/
13	47, male	2018	Compulsive eating Features of hypersexuality	Stalevo®	/

*Age (years) at time of study

Several different hypotheses have been suggested to explain the aetiopathogenesis of ICDs. One hypothesis suggests that impulsivity can occur through the stimulation of the STN and neighbouring tracts, through changes in the processing of associative and limbic information towards cortical and subcortical regions.^{15,16} Furthermore, minimal changes in stimulation site and parameters can also lead to different effects. For example, stimulation of the most superior contact within the STN nucleus produces greater effects on decision-making tasks than stimulation of the deepest contact.¹⁷

Another explanation for the development of impulsivity following DBS insertion is microtrauma during the surgical procedure that may result in damage to the STN or its neighbouring structures associated with motivational behaviours.¹⁴

In medically treated patients, higher levodopa dosages are associated with the development of ICDs. Therefore, another postulated hypothesis is that patients who undergo DBS insertion have a total higher cumulative exposure to dopaminergic medication due to longer disease duration and

greater disease severity, contributing to the development of such behaviour.¹⁴

Postoperative dopaminergic therapy reduction, or lack thereof, is also likely to play an important role. Polyvios et al showed that patients who remained on dopaminergic medication postoperatively were more likely to exhibit ICDs.¹⁸ Similarly, in a cross-sectional study by Weintraub et al, patients who remained on dopaminergic medication postoperatively had a poorer outcome in terms of ICDs, when compared to patients in whom dopaminergic treatment was reduced. This is possibly because DBS can sensitize the brain to the behavioural effects of dopamine replacement therapy, especially on an existing background of high impulsivity.¹⁹ Djamshidian et al showed that patients treated with dopamine agonists made significantly more irrational choices than patients who were not on such drugs, with this study also concluding that STN-DBS has no effect in this task.²⁰

It has also been suggested that improvement of motor function following DBS surgery facilitates the full expression of behavioural abnormalities that have developed secondary to pre-operative dopamine replacement therapy.²¹

Several limitations were identified in this analysis. Firstly, the cohort of patients was relatively small, with the total number of eligible patients being 38, of which 36 participated. The high questionnaire return rate is a clear strength in this analysis, as 95% of the patients identified participated. This is significant in that the analysis is free of recruitment bias and so gives a clear snapshot of our patient population.

Furthermore, patients may have been subject to response bias as the study was carried out by having patients answer a questionnaire. Also, there was no standardised assessment of pre-operative ICDs in our cohort of patients, making the exclusion of pre-operative ICDs subject to recall bias.

This analysis is a snapshot of DBS patients in our centre, highlighting the reality of ICDs in this patient population. Future work focusing on prospective groups of PD patients who are planned to undergo surgery compared with a control group of non-surgical patients may be more revealing of the true relationship between ICDs and STN-DBS.

CONCLUSION

This analysis confirms that a substantial number of patients suffer from ICDs following chronic STN-DBS. This highlights the importance of screening for ICDs, both prior to DBS surgery and post-operatively during regular follow-up visits, as this would allow a more holistic, effective, and appropriate management of the impulsive behaviours.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Ludvic Zrinzo MD PhD FRCS for the guidance provided when writing the manuscript and for the specialised neurosurgical procedures and visiting clinics he performs at Mater Dei Hospital.

REFERENCES

1. DeLong MR, Wichmann T. Basal Ganglia Circuits as Targets for Neuromodulation in Parkinson Disease. *JAMA Neurol.* 2015;72:(1)1354-60.
2. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord.* 2006;21 Suppl 14:290-304.
3. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology.* 2012;79:(1)55-65.
4. Castrioto A, Lozano AM, Poon YY, et al. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol.* 2011;68:(12)1550-6.
5. Abbes M, Lhommée E, Thobois S, et al. Subthalamic stimulation and neuropsychiatric symptoms in Parkinson's disease: results from a long-term follow-up cohort study. *J Neurol Neurosurg Psychiatry.* 2018;89:(8)836-43.
6. Gatto EM, Aldinio V. Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. *Front Neurol.* 2019;10:351.

7. Maloney EM, Djamshidian A, O'Sullivan SS. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations. *J Neurol Sci.* 2017;374:47-52.
8. Cossu G, Rinaldi R, Colosimo C. The rise and fall of impulse control behavior disorders. *Parkinsonism Relat Disord.* 2018;46:S24-9.
9. Vela L, Martínez Castrillo JC, García Ruiz P, et al. The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study. *J Neurol Sci.* 2016;368:150-4.
10. Turner J. Parkinson's Measurement [Internet]. [cited 2022 Jan 5]. Available from: <https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm>
11. Merola A, Romagnolo A, Rizzi L, et al. Impulse control behaviors and subthalamic deep brain stimulation in Parkinson disease. *J Neurol.* 2017;264:(1)40-8.
12. Kim YE, Kim HJ, Kim HJ, et al. Impulse control and related behaviors after bilateral subthalamic stimulation in patients with Parkinson's disease. *J Clin Neurosci.* 2013;20:(7)964-9.
13. Hälbjerg TD, Tse W, Frisina PG, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. *Eur J Neurol.* 2009;16:(4)493-7.
14. Amami P, Dekker I, Piacentini S, et al. Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up. *J Neurol Neurosurg Psychiatry.* 2015;86:(5)562-4.
15. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev.* 1995;20:(1)128-54.
16. Temel Y, Kessels A, Tan S, et al. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat Disord.* 2006;12:(5)265-72.
17. Smeding HM, Goudriaan AE, Foncke EM, et al. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. *J Neurol Neurosurg Psychiatry.* 2007;78:(5)517-9.
18. Polyvios D, Rickards H, Cavanna AE. Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. *Parkinson's Dis.* 2011;2011:1-6.
19. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol.* 2010;67:(5)589-95.
20. Djamshidian A, O'Sullivan S, Foltynie T, et al. Dopamine agonists rather than deep brain stimulation cause reflection impulsivity in Parkinson's disease. *J Parkinsons Dis.* 2013;3:(2)139-44.
21. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatry.* 2002;72:(6)701-7.