Predictors of short-term impulsive and compulsive behaviour after subthalamic stimulation in Parkinson disease

Anna Sauerbier,1,2 Philipp Loehrer,3 Stefanie T. Jost,2 Shania Heil,2 Jan N. Petry-Schmelzer,2,4 Johanna Herberg,2 Pia Bachem,2 Salima Aloui,2 Alexandra Gronostaj,2 Lisa Klingelhofer,2,6 J. Carlos Baldermann,2,5 Daniel Huys,5 Christopher Nimsky,6 Michael T. Barbe,2 Gereon R. Fink,2,7 Pablo Martinez-Martin,8 K. Ray Chaudhuri,1,9,10 Veerle Visser-Vandewalle,11 Lars Timmermann,3 Daniel Weintraub,12 Haidar S. Dafsari1,2 On behalf of EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson’s Disease Study Group

ABSTRACT

Background The effects of subthalamic stimulation (subthalamic nucleus–deep brain stimulation, STN-DBS) on impulsive and compulsive behaviours (ICB) in Parkinson’s disease (PD) are understudied.

Objective To investigate clinical predictors of STN-DBS effects on ICB.

Methods In this prospective, open-label, multicentre study in patients with PD undergoing bilateral STN-DBS, we assessed patients preoperatively and at 6-month follow-up postoperatively. Clinical scales included the Questionnaire for Impulsive-Compulsive Disorders in PD Scale (QUIP-RS), PD Questionnaire-8, Non-Motor Symptom Scale (NMSS), Unified PD Rating Scale in addition to levodopa-equivalent daily dose total (LEDD-total) and dopamine agonists (LEDD-DA). Changes at follow-up were analysed with Wilcoxon signed-rank test and corrected for multiple comparisons (Bonferroni method). We explored predictors of QUIP-RS changes using correlations and linear regressions. Finally, we dichotomised patients into ‘QUIP-RS improvement or worsening’ and analysed between-group differences.

Results We included 55 patients aged 61.7 years±8.4 with 9.8 years±4.6 PD duration. QUIP-RS cut-offs and psychiatric assessments identified patients with preoperative ICB. In patients with ICB, QUIP-RS improved significantly. However, we observed considerable interindividual variability of clinically relevant QUIP-RS outcomes as 27.3% experienced worsening and 29.1% an improvement. In post hoc analyses, higher baseline QUIP-RS and lower baseline LEDD-DA were associated with greater QUIP-RS improvements. Additionally, the ‘QUIP-RS worsening’ group had more severe baseline impairment in the NMSS attention/memory domain.

Conclusions Our results show favourable ICB outcomes in patients with higher preoperative ICB severity and lower preoperative DA doses, and worse outcomes in patients with more severe baseline attention/memory deficits. These findings emphasise the need for comprehensive non-motor and motor symptoms assessments in patients undergoing STN-DBS.

Trial registration number DRKS00006735.

INTRODUCTION

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-established treatment in patients with advanced Parkinson’s disease (PD), improving quality of life, motor and non-motor symptoms (NMS).1,2 Specifically, STN-DBS can influence neuropsychiatric symptoms, such as depression, anxiety, alexithymia, impulsivity and compulsivity.1,4,6 Currently available data on the effect of DBS on impulsive and compulsive behaviours (ICB) are contrasting, with much methodological heterogeneity.7,8 One of the main reported risk factors of ICB in PD is dopamine replacement therapy, particularly dopamine agonists (DA), which is possibly related to an overstimulation of the mesolimbic dopaminergic system.9 As STN-DBS typically leads to a significant decrease in dopaminergic medication, that is, lower levodopa equivalent daily dose (LEDD), postoperative improvement in ICB has been observed.8,10–13 However, studies have shown that the effect of STN-DBS on ICB is complex and goes beyond LEDD reduction, with possible adding factors including preoperative clinical aspects.8,14 Understanding the factors contributing to changes in ICB could be critical for improving patient selection for DBS.

Therefore, our study’s main objective was to identify clinical predictors of the effect of STN-DBS on ICB. We hypothesised that higher preoperative ICB and LEDD-DA would be predictors of beneficial postoperative ICB changes.

MATERIALS AND METHODS

Study design

This study is a prospective, observational real-life study with a 6-month follow-up including patients with PD undergoing STN-DBS. Consecutive patients were screened between August 2015 and March 2020.

Participants

The diagnosis of PD was based on the UK Brain Bank criteria. Patients were screened for DBS...
treatment according to the guidelines of the International PD and Movement Disorders Society and required a sufficient levodopa responsiveness (>30% improvement in the Unified PD Rating Scale-III, UPDRS). Surgical procedures are described elsewhere.\(^{15}\)

### Clinical assessment

Clinical assessments were performed at preoperative baseline (MedON) and at 6-month follow-up after DBS surgery (MedON/StimON).

Assessments included:

- Impulsive and compulsive behaviours
  - The Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS)\(^{16}\) assessed ICB during the previous 4 weeks. The QUIP-RS contains a 4×7 structure with four primary questions (about commonly reported thoughts, urges/desires and behaviours associated with ICB), each applied to seven items: (1) The first four items address impulse control disorder (ICDs) (gambling, buying, sexual and eating behaviours), (2) Items 5 and 6 assess other compulsive behaviours (punding and hobbyism) and (3) Item 7 assesses compulsive medication use. In each of the four primary questions, all seven items are scored on a five-point Likert scale from 0 (never) to 4 (very often). Therefore, the QUIP-RS total score ranges from 0 to 112. To ascertain if the reported symptoms were clinically relevant, we used the previously published cut-off scores.\(^{17}\) The cut-off for ICDs (items 1–4) was a total score ≥10, and for other compulsive behaviours (items 5 and 6) ≥7. A cut-off score for compulsive medication use has not been established yet, due to its low prevalence in some PD populations.\(^{18}\)

- Additionally, expert psychiatrists specialised in examinations of patients with PD interviewed patients focusing on ICB.

- Secondary outcomes included:

- Pre-DBS and post-DBS clinical characteristics
  - The Median baseline HY stage was 2 (IQR 2–3).
  - The median baseline UPDRS domains range from 0 (no impairment) to 360 (maximum NMS impairment).

- Statistical analysis
  - Gaussian distribution of test scores was assessed using the Shapiro-Wilk method. Wilcoxon signed-rank tests, respectively, paired t-tests, if parametric test criteria were fulfilled, were employed to test for changes at 6-month follow-up. This analysis was performed in the overall cohort and the subgroup of patients who experienced clinically relevant baseline ICB. We corrected for multiple comparisons using the Bonferroni method and report adjusted p-values at the significance threshold of 0.05. Post hoc, the relationship between preoperative clinical outcome parameters and QUIP-RS score changes were explored using Spearman correlations. The QUIP-RS change score (mean \(T\)\(^{\text{Baseline}}\) – mean \(T\)\(^{\text{Follow-up}}\)) was correlated with the following baseline variables: age, disease duration since diagnosis, QUIP-RS, PDQ-8 SI, NMSS total score, NMSS domains, UPDRS part II to IV, LEDD total and LEDD-DA. The correlations were graded between 0.0 and 0.19 ‘very weak’, 0.20–0.39 ‘weak’ 0.40–0.59 ‘moderate’, 0.60–0.79 ‘strong’ and 0.80–1.0 ‘very strong’.\(^{21}\) Positive correlations indicate that higher baseline values are associated with more postoperative QUIP-RS improvement.

- To identify clinical predictors of ICB after STN-DBS, we analysed stepwise linear regressions. We included QUIP-RS change score as the criterion variable and parameters from the correlation analyses with a relaxed threshold (\(p<0.25\)) as candidate predictor variables.\(^{22}\) Multicollinearity was checked using intercorrelations between candidate predictor variables (\(r>0.6\)) and variance inflation factors, which should not exceed 10.\(^{23}\)

- To confirm the feasibility of identified predictors and explore between-group differences, we dichotomised the QUIP-RS changes and defined groups of patients experiencing a clinically relevant ‘QUIP-RS improvement’ and ‘QUIP-RS worsening’ based on a designated threshold of ½ SD of QUIP-RS total at baseline. This cohort-derived threshold was used in several previous studies.\(^{13,24}\)

- Patients who experienced no clinically relevant improvement or worsening of QUIP-RS changes were not included in this analysis. Differences between these two groups were tested using Mann-Whitney U tests.

All analyses were conducted using SPSS V.26.0 for Mac.

### RESULTS

In total, 55 patients (69.1% male) were included with a mean age of 61.7 years (±8.5 SD) and a mean disease duration of 9.8 years (±4.6 SD). The median baseline HY stage was 2 (IQR 2–3).

### Pre-DBS and post-DBS clinical characteristics

At baseline, 38.9% of patients reported ICB. Among those, 16.2% reported eating disorders, 5.4% hypersexuality, 5.4% excessive shopping, none gambling problems and 31.4% reported punding and hobbyism.

Clinical characteristics at baseline and 6-month follow-up are presented in Table 1.

In the overall cohort, the main outcome QUIP-RS total score did not change at follow-up. However, in the subgroup of patients reporting clinically relevant preoperative ICB, the QUIP-RS total improved significantly at follow-up (30.5±10.7 before vs 24.1±14.0 afterward, \(p=0.044\)).

In the overall cohort, secondary outcomes including PDQ-8 SI, NMSS total, UPDRS-II, UPDRS-IV, HY, LEDD total and LEDD-DA improved significantly from baseline to 6-month follow-up. In the subgroup of patients experiencing preoperative ICB, secondary outcomes including NMSS total, LEDD total and LEDD-DA improved significantly and a trend was observed.
for PDQ-8 SI and UPDRS-IV. In contrast to the overall cohort, the UPDRS-II outcome was not significant.

Correlation analyses
In the overall cohort, Spearman correlations between baseline clinical outcome parameters and the QUIP-RS change score resulted in significant correlations for the higher baseline QUIP-RS total score ($r_s=0.454, p=0.001$; ‘moderate’) and the lower baseline LEDD-DA ($r_s=0.351, p=0.009$; ‘weak’). There were no significant correlations between the QUIP-RS change score and baseline NMSS mood/apathy domain (all $p>0.05$). QUIP-RS change score was not significantly correlated with LEDD total or LEDD-DA changes in the overall cohort and in patients with ICB at baseline (all $p>0.05$). Exploring the relationship of LEDD-DA changes and preoperative NMSS domain scores, we found no significant correlations with the attention/memory and mood/apathy domain scores (all $p>0.05$).

Predictor analysis
Univariate linear regression analyses with change in QUIP-RS total score as the criterion variable were performed using candidate predictor variables identified in correlation analyses (relaxed threshold $p<0.25$).28 Besides LEDD-DA and QUIP-RS total score, at the relaxed inclusion threshold, this included the NMSS attention/memory domain ($r_s=-0.187, p=0.171$) and UPDRS-III ($r_s=-0.212, p=0.139$). Significant predictor variables were the QUIP-RS total score ($\beta=0.353, p=0.008$) and LEDD-DA ($\beta=-0.342, p=0.010$).

The model accounted for 22.4% of the variance ($R^2=0.224$, in QUIP-RS change ($F_{2,46}=7.936, p<0.001$).

Difference between ‘QUIP-RS improvement’ and ‘QUIP-RS worsening’ groups
The cut-off for a clinically relevant change in QUIP-RS total score was 6.55 points according to the designated threshold $\frac{1}{2}$ SD of baseline QUIP-RS total score. Out of 55 patients in the overall cohort, 16 patients (29.1%) experienced a clinically relevant improvement and 15 patients (27.3%) a clinically relevant worsening in the QUIP-RS total score. In 24 patients (43.6%), ICB symptoms were stable.

In the overall cohort, in the ‘QUIP-RS worsening’ group compared with the ‘QUIP-RS improvement’ group, we observed at baseline higher LEDD-DA (321.9 mg $\pm$139.2 vs 180.3 mg $\pm$156.1, $p=0.021$), a lower QUIP-RS total (12.1 $\pm$13.6 vs 21.8 $\pm$10.6, $p=0.009$) and higher NMSS attention/memory domain scores (5.1 $\pm$4.4 vs 2.8 $\pm$5.1, $p=0.043$).

In the cohort of 14 patients reporting clinically relevant preoperative ICB, a clinically relevant improvement was observed in six patients (median baseline QUIP-RS score: 29.5, IQR: 21.5–40.25) and worsening in one patient (median baseline QUIP-RS score: 48), whereas QUIP-RS changes remained stable in seven patients (median baseline QUIP-RS score 24.0, IQR: 20–36).

DISCUSSION
In the present study, we assessed clinical aspects predicting ICB in 55 patients with PD undergoing STN-DBS. The QUIP-RS total score improved significantly in patients experiencing preoperative ICB. Furthermore, we observed considerable inter-individual variability of QUIP-RS outcomes as 27.3% of patients experienced a clinically relevant worsening and 29.1% a clinically relevant improvement. Post hoc analyses revealed that higher baseline QUIP-RS and lower baseline LEDD-DA were associated with greater QUIP-RS improvements.

Quality of life, NMS and motor symptoms, and medication requirements in the overall cohort
Following previous studies, we observed a postoperative improvement of quality of life, non-motor, and motor symptoms, and reduced total dopaminergic medication and DA in the overall cohort.1 31 32

Impulsive and compulsive behaviour
Prevalence and severity
In our cohort, 39% of patients reported ICB at baseline, with hobbies and shopping being the most frequent, followed by eating disorders, excessive shopping and hypersexuality. These findings agree with previous studies in DBS populations.3 33 34 Moreover, as in previous studies, we observed considerable inter-individual variability of postoperative changes of ICB. There was no linear trend with 27.3% of patients experiencing a clinically relevant worsening and 29.1% a clinically relevant improvement.2 24 33

To our knowledge, this is among one of the first studies analysing a wide range of motor and non-motor predictors for ICB. We found that a higher QUIP-RS total score is the strongest predictor for greater improvements in postoperative QUIP-RS score. Notably, we found a significant improvement in the QUIP-RS in patients reporting clinically relevant preoperative ICB. A study by Rossi et al reported a trend for QUIP-RS improvement in patients with higher preoperative ICB. The significance threshold may have been missed in that study as they...
included a smaller cohort size (n=37).33 In contrast, Moum et al reported that preoperative ICB resolved postoperatively in 2/7 patients, whereas 17 patients developed newly diagnosed ICB postoperatively.35 However, this was only a retrospective analysis, and the study cohort was not homogeneous as unilaterally and bilaterally implanted patients in different DBS targets (STN and globus pallidus internus) were included.

Motor symptoms and dopaminergic medication
Consistent with previous studies, we did not find an effect of the preoperative motor score (UPDRS-III) on postoperative ICB changes.7 Moreover, we found that lower LEDD-DA was a predictor for greater improvement in QUIP-RS total score. A possible explanation might be that patients with higher tendency to develop ICB, may be unable to tolerate higher doses of DA,16 37 perhaps prompting surgical evaluation. However, the change in LEDD total and LEDD-DA was not associated with a change in QUIP-RS total score, even in the population with ICB at baseline. This lack of association may result from a non-linear relationship of LEDD and severity of ICB, which may be based on patient-specific thresholds of the dopaminergic medication causing ICB. Previous studies reported the missing correlation between LEDD changes and ICB outcome, which underlines that the DBS effect on ICB appears not solely to be based on dopaminergic treatment.

Attention/memory and other NMS
Furthermore, the present study is the first to report a relationship between more severe preoperative attention/memory deficits and a clinically relevant postoperative worsening of ICB. This finding suggests that neuropsychological deficits are detrimental to ICB outcomes. This result complements a recent multicentre study reporting more severe ICB in demented compared with non-demented patients with PD.38 Our study expands the observations by Kim et al who reported in a cross-sectional analysis more severe cognitive impairment (worse Mini-Mental State Examination score) in patients with worsened or de novo development of ICB retrospectively assessed with the QUIP-RS after STN-DBS. However, in contrast to this study, we found no significant association between higher preoperative mood disorders assessed with the NMSS mood/apathy domain and greater improvement of impulsivity and compulsivity. Kim et al used the Beck Depression Inventory, which might be more sensitive to smaller differences in depression symptoms than the NMSS, which we used in the present study. Furthermore, a recent study by des Neiges Satin et al reported a higher risk of developing ICD post STN-DBS in patients with apathy preoperatively, a finding that we did not confirm with our data.39 The authors used the Ardouin Scale of Behaviour which might be more sensitive to capture apathy than the NMSS.

Our group’s previous study provided evidence for a ‘sweet spot’ for beneficial effects of STN-DBS on attention/memory,4 and Mosley et al report the connectivity profile of DBS effects on impulsivity and compulsivity. Assuming the underlying pathomechanisms of these symptoms are connected through common neural correlates, future studies are needed to investigate common connectivity profiles of STN-DBS effects on attention, memory, mood, impulsivity and compulsivity. This information may help DBS programming in patients with concomitant preoperative neuropsychological symptoms and ICB.

Limitations
There are several limitations to this study. ICBs, which are not caused by dopaminergic medication, are considered a contraindication for DBS, and our results cannot be applied to patients experiencing these. Furthermore, our study’s population size was relatively small with 55 patients, few of which experienced clinically relevant ICB at baseline or clinically relevant postoperative improvement or worsening of ICB. Follow-up assessments in the present study were conducted 6 months after surgery. Previous studies have shown that ICB can occur at long-term follow-up in patients treated with DA.40 Further studies are warranted to address the long-term effects of STN-DBS on ICB. The multicentre design of our study is likely to reduce the potential bias of a single-centre design. In this study, we did not analyse DBS settings or volume of tissue activated by DBS, as we were interested in preoperative clinical predictors of ICB outcomes. Furthermore, caregiver reports were not assessed no additional behavioural tasks were investigated to corroborate verbal QUIP-RS reports. The QUIP-RS surveys symptoms over the previous 4 weeks, including motor ON and OFF states. In this analysis, we opted to calculate a cut-off value for the classification of clinically relevant ‘QUIP-RS improvement’ and ‘QUIP-RS worsening’ based on a previously published cohort-specific specific threshold (½ SD of testbaseline). To our knowledge, minimal clinically significant differences have not yet been determined for the QUIP-RS. We used a distribution-based method because DBS cohorts include highly selected patient populations, resulting in considerable differences of baseline ICB compared with the general population of patients with PD.41 Distribution-based methods seek to determine minimal clinically important differences based on the observed scores and, therefore, they simply express the change in a standardised way.41 A disadvantage of the anchor-based methods is the possibility that the minimal clinically important difference falls within the instrument’s random variation and the susceptibility of some ratings to recall bias.42 43 Furthermore, future studies are needed to investigate if neuroimaging of the dopaminergic and possibly also the cholinergic system may provide objective biomarkers for the identification of patients who are at risk of developing ICB, in particular when concomitant attention/memory deficits are observed.

CONCLUSION
In this study, we observed favourable ICB outcomes in patients with higher preoperative ICB burden and lower doses of DA, whereas more severe preoperative attention/memory deficits were associated with clinically relevant ICB worsening after STN-DBS. This study’s novel findings highlight the importance of a comprehensive assessment of patients’ motor and non-motor profiles before DBS surgery. Further studies in larger cohorts analysing a wide range of motor and NMS may better predict patients’ postoperative risk of developing ICDs. The overall aim of this line of research is a better selection of patients for DBS therapy.44

Author affiliations
1Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK
2Department of Neurology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
3Department of Neurology, University of Marburg and University Hospital Giessen and Marburg, Campus Marburg, Marburg, Germany
4Department of Neurology, University of Dresden and University Hospital Dresden, Dresden, Germany
5Department of Psychiatry, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
6Department of Neurosurgery, University of Marburg and University Hospital Giessen and Marburg, Campus Marburg, Marburg, Germany
7Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Center Jülich, Jülich, Germany

Movement disorders


J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp-2021-326131 on 11 September 2021. Downloaded from http://jnnp.bmj.com/ on October 7, 2023 by guest. Protected by
Acknowledgements The study centre Marburg (PAL, CN, LJ) acknowledges Dr. D.J. Pedrosa for the allocation of patients to different research projects including the present study.

Contributors AS: data acquisition and analysis, drafting of the manuscript. PL: data acquisition, critical revision of the manuscript. ST: data acquisition, critical revision of the manuscript. SH: data acquisition, critical revision of the manuscript. JNP-S: data acquisition, critical revision of the manuscript. AHG: data acquisition, critical revision of the manuscript. AG: data acquisition, critical revision of the manuscript. UC: patient recruitment, critical revision of the manuscript. JPC: psychiatric assessments, critical revision of the manuscript. CG: psychometric assessments, critical revision of the manuscript. MB: critical revision of the manuscript. GRF: critical revision of the manuscript. PM-M: study concept and design, critical revision of the manuscript. KRM: study concept and design, critical revision of the manuscript. VV-V: surgical intervention, critical revision of the manuscript. LT: study concept and design, critical revision of the manuscript. DW: critical revision of the manuscript. HSD: study concept and design, data acquisition and analysis, drafting and critical revision of the manuscript.

Funding This manuscript presents independent research funded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King’s College London and Parkinson’s UK. Funding ID Parkinson’s UK K 1406

Disclaimer The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, Parkinson’s UK or the Department of Health.

Competing interests AS is funded by the GusuY programme of the Medical Faculty of the University of Cologne and has received funding from the Prof. Klaus Thiemann Foundation. PL was funded by the SUCCESS-Programme of the University of Marburg, the Parkinson’s Foundation and the Stiftung zur Förderung junger Neurowissenschafetler. STI was funded by the Prof. Klaus Thiemann Foundation. JNP-S has received travel grants from Boston Scientific. LH reports academic grants from EU Horizon 2020 and from the excellence strategy of the Technical University Dresden, Germany; habilitation funding for women from the Medical Faculty of the Technical University Dresden, Germany; Medicor GmbH, Berlin, Germany; and from the German Research Foundation (DFG). KPC serves as an editorial board member of Cortex, Neurological Research and Practice, NeuroImage: Clinical, Zeitschrift für Neuropsychologie, and DGNeuropsychologie, receives royalties from the publication of the books Funktionelle MRT in Psychiatrie und Neurologie, Neurologische Differentialdiagnostik and SOP Neurologie; received honoraria for speaking engagements from Bayer, Deprix, Ergo KV, Forum für medizinische Fortbildung FormF, GSK, Medica Academy Messe Düsseldorf, Medbrain Healthcare, Novartis, Pfizer and Sportärztetubad NRW; PM-M has received honoraria from Editorial Vigura and Takeda Pharmaceuticals for lecturing in courses; from Britannia for writing an article in their Parkinson’s Disease Medical Journal-Kinetik; and from the International Parkinson and Movement Disorder Society (MDS) for management of the Programme on Rating Scales. Grants from the MDS for development and validation of the MDS-NMS, KRC has received funding from Parkinson’s UK (funding ID Parkinson’s UK K 1406), NIH, UCBB and the European Union; he received honoraria from UCBB, Abbott, Britannia, US Worldmeds, and Otsuka Pharmaceuticals; and acted as a consultant for AbbVie, UCBB and Britanna. VV-V is a member of the advisory boards and reports consultancies for Boston Scientific. LT reports grants, personal fees and non-financial support from SAPIENS Steering Brain Stimulation, Medtronic, Boston Scientific, Abbott and St. Jude Medical. DW reports no financial disclosures. JSK was funded by the EU Joint Programme – Neurodegenerative Research (JPND), the Prof. Klaus Thiemann Foundation, and the Feldgenhauser Foundation and has received honoraria by Boston Scientific, Medtronic and Stadapharm.

Patient consent for publication Not required.

Ethics approval All patients gave written informed consent before being included.

The study was conducted under the Declaration of Helsinki. Local ethics committees approved the study protocols (Cologne study no.: 12–145; Marburg study no.: 155/17).

REFERENCES

Movement disorders


