A systematic review of body mass gain after deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease

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Summary
This systematic review investigated the effects of deep brain stimulation of the subthalamic nucleus on extent and time course of body mass changes in patients with Parkinson's disease. A computerized search identified relevant articles using a priori defined inclusion and exclusion criteria. A descriptive analysis was calculated for the main outcome parameters body mass and BMI. Thirty-eight out of 206 studies fulfilled the inclusion criteria (979 patients aged 59.0±7.5 years). Considering the longest follow-up time for each study, body mass and BMI showed a mean increase across studies of +5.71kg (p < .0001; d = 0.64) and +1.8kg/m² (p < .0001; d = 1.61). The time course of body mass gain revealed a continuous increase ranging from +3.25kg (d = 0.69) at 3 months, +3.88kg (d = 0.21) at 6 months, +6.35kg (d = 0.72) at 12 months, and +6.11kg (d = 1.02) greater than 12 months. Changes in BMI were associated with changes in disease severity (r = 0.502, p = .010) and pharmacological treatment (r = 0.440, p = .0231). Data suggest that body mass gain is one of the most common side effects of deep brain stimulation going beyond normalization of preoperative weight loss. Considering the negative health implications of overweight, we recommend the development of tailored therapies to prevent overweight and associated metabolic disorders following this treatment.

KEYWORDS
deep brain stimulation, Parkinson’s disease, subthalamic nucleus, weight gain
1 | INTRODUCTION

Body mass changes in both directions, weight loss and weight gain, have been reported in patients with Parkinson's disease (PD)1 and are often observed in response to treatment. Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus internus (GPi) is an efficient treatment option for severe motor complications in advanced PD. Hence, DBS significantly improves motor and non-motor fluctuations, rest tremor, dyskinesias as well as quality of life (QoL), and usually results in a decrease of dopaminergic medications.2-7 Side effects may include speech disturbance, postural instability, mood changes, and significant body mass gain independent of the DBS target region.8-10 The extent and time course of body mass gain after DBS surgery have not yet been systematically addressed11 although some potential mechanisms of body mass gain have been suggested like improvement of resting tremor and dyskinesias,4,12 reduction in energy expenditure,13,14 changes in eating behaviour and food intake12,15-20 as well as alterations in hypothalamic adipokine release.10,18,19,21-23

The purpose of this study is to systematically analyze the extent and range of body mass gain after STN DBS. We selected available studies investigating postoperative body mass changes and conducted a systematic review to quantify stimulation-induced body mass changes. We aimed to clarify i) the magnitude of the relationship between STN DBS and body mass gain, ii) the extent of body mass gain and BMI gain, and iii) the time course of assumed body mass and BMI gain.

2 | METHODS

2.1 | Search Strategy

A systematic review was conducted on original studies that assessed body mass gain in patients with PD after STN DBS, following the PRISMA recommendations. A computerized search for all STN DBS studies in PD was performed in MEDLINE, Cochrane Library, Clinical Trials, and Livivio containing the following search terms (last search performed on November 11th, 2017): (((Parkinson OR Parkinson's disease) OR (PD)) AND (((weight OR (BMI)) AND ((change) OR (gain) OR (increase))) AND ((STN DBS) OR (Subthalamic nucleus deep brain stimulation) OR (deep brain stimulation) OR (DBS) OR (GPi deep brain stimulation) OR (globus pallidus deep brain stimulation) OR (palilial deep brain stimulation)))). Search was performed for articles published between 1984 and 2017 and was restricted to English and German publications, but not to age and gender of subjects, as well as origin of publication.

2.2 | Study Selection and Data Collection

All abstracts and articles of the computerized search were independently screened by two investigators (JS, BW) for potential relevance. Any disagreements were resolved by further examination of a third investigator (NB) and via consensus.

The following studies were excluded: reviews, letters, commentaries, abstracts, posters, case reports, correspondences to articles, and double nominations of publications in different search portals. Furthermore, animal studies, studies including DBS of the GPi, ventral intermediate thalamic nucleus (VIM) or caudal zona incerta (cZi), studies with alternative surgical methods (e.g. pallidotomy), articles reporting non-weight related outcomes, studies assessing body mass gain in another disease and studies targeting other research questions were not considered.

The included studies had to contain at least one of the following outcomes: absolute body mass before and after STN DBS or body mass changes, absolute body mass index (BMI) before and after STN DBS or BMI changes. Normal weight (BMI: 18.5-24.9 kg/m²), overweight (BMI: 25.0-29.9 kg/m²) and obesity were defined according to the WHO definition. THE WHO defines overweight and obesity for adults as follows: overweight is a BMI greater than or equal to 25 and obesity is a BMI greater than or equal to 30.24 Additionally, UPDRS III and IV scores, as well as levodopa equivalent doses (LEDD) were investigated to reveal the efficacy of the DBS treatment. Moreover, sufficiently specified numerical baseline and follow-up outcome data for body mass, BMI, UPDRS III, UPDRS IV, and LEDD were required as well as data on standard deviations (SD) or standard errors of the mean.

2.3 | Statistical analyses

Results are reported as mean ± SD. Data were analyzed using Excel Version 2016 (Microsoft, Redmond, WA), SPSS Statistics 22.0 (SPSS Inc, Chicago, IL), and GraphPad Prism version 7.03 (GraphPad Software, La Jolla, CA) for Windows®. Paired Student's t-test was used to test for changes in BMI, BM, UPDRS III and IV, and LEDD. The effect size of BM and BMI changes were described by Cohen’s d. Variables associated with changes in the main dependent variables (i.e. BM, BMI) were analyzed by Pearson correlation. Missing outcome data and SDs were calculated if applicable. All results were considered as statistically significant at the 5% level.

3 | RESULTS

3.1 | Study Selection and Characteristics

The literature search identified 206 potentially relevant articles of which 154 studies were assessed for a more detailed evaluation (Figure 1). Following the selection process, 54 studies1,2,4,6,8-10,12,21,23,25-58 fulfilled the inclusion criteria as described above. For the analysis, 38 studies could be included of which 18 (47%) were prospective case studies, 12 (32%) were prospective case-control studies, 4 (11%) were retrospective case studies, 2 (5%) were retrospective case-control studies, 1 (2.5%) was a cross-sectional, and 1 (2.5%) was a retrospective survey study. In sum, the 38 selected studies included 979 patients with PD and STN DBS and 287 controls comprising of non-stimulated patients with PD under medical treatment (N = 186) and healthy control subjects (N = 101).
3.2 | Patient characteristics

Table 1 provides demographic information on subjects from each study. Study sample sizes ranged from 7 to 57 subjects (mean, 25.8 ± 11.6; N = 979) with a follow-up time between 1 month to 60 months after DBS implantation (mean, 17.8 ± 15.2 months). The mean age across studies was 59.0 ± 7.5 years (range, 54.9 – 66.0 years; N = 833). The mean disease duration prior to surgery was 12.4 ± 4.0 years (range, 8.5 years – 15.7 years; N = 680) at baseline. There was no specification of ethnicity of subjects in the studies.

3.3 | Body mass change

On average, we identified increases in body mass during the entire period. The analysis revealed a significant body mass gain in 21/21 studies (100%) with complete data sets at the latest follow-up. 1,4,8,13-15,23,28,30,32,40-44,46,49,54 The overall pooled mean body mass gain was +5.71 kg (baseline weight, 73.25 kg; range body mass gain, 1.30 kg – 11.10 kg; 95% CI, -6.69, -4.74; N = 446; p < .0001; Figure 2) with a corresponding effect size of d = 0.64 (Suppl. material). To minimize a potential bias, a secondary analysis for different postoperative time points was performed at 3, 6, 12 months and greater than 12 months follow-up time.

The mean body mass gain 3 months after surgery was +3.25 kg (baseline weight, 73.70 kg; range body mass gain, 1.10 kg - 5.90 kg; 95% CI, -4.32, -2.18; N = 190; p < .001) with a corresponding effect size of d = 0.66. Mean change in body mass from baseline to 6 months following DBS was +3.88 kg (baseline weight, 74.98 kg; range body mass gain, 2.64 kg - 5.50 kg; 95% CI, -5.09, -2.68; N = 127; p < .001; d = 0.22). At 12 months follow-up, body mass increased by +6.35 kg (baseline weight, 71.39 kg; range body mass, 2.90 kg - 11.10 kg; 95% CI, -7.99, -4.71; N = 241; p < .0001; d = 0.72). Greater than 12 months follow-up, body mass gain remained stable with +6.11 kg (baseline weight, 69.23 kg; range body mass gain, 4.90 kg - 8.10 kg; 95% CI, -8.32, -3.91; N = 66; p = .003; d = 1.02).

3.4 | Change in BMI

Nineteen studies (N = 512) were available for the assessment of the BMI. All studies revealed an increase in BMI for the latest follow-up. 1,4,6,13-15,23,28,30,32,40-44,46,49,54 The overall pooled mean increase in BMI was +1.83 kg/m² (baseline BMI, 24.84; range BMI gain, 0.40-3.20 kg/m²; 95% CI, -2.33, -1.31; p < .0001) with a mean effect size of d = 1.61 (Suppl. material) for the latest follow-up. The share of patients with overweight (BMI 25.0-29.9 kg/m²) increased from 40% to 78%, and thus the share of patients with normal weight decreased from 60% to 22%.
| Reference       | Year | Study type                | Stimulation Target | N enrolled | Mean follow-up (months) | Mean age at surgery (yrs) | Mean disease duration before surgery (yrs) | Mean preoperative levodopa dose (mg) | Mean increase of body mass (kg) | Mean effect size of body mass gain (Cohens’ d) |
|-----------------|------|--------------------------|--------------------|------------|-------------------------|---------------------------|--------------------------------------------|--------------------------------------|---------------------------------|--------------------------------------|
| Aiello et al.   | 2017 | Prospective case-control study | bilateral STN DBS | 18         | 6                       | 60.17 ± 6.9               | 9.77 ± 4.19                              | 1113.56 ± 436.35                      | 2.64                            | 0.14                                 |
| Balestrino et al. | 2017 | Prospective case study | bilateral STN DBS | 32         | 12                      | 60 ± 7                    | 12 ± 4                             | 1111.6 ± 396.7                         | 6.7 ± 5.0                       | 0.49                                 |
| Bannier et al.  | 2009 | Prospective case study | bilateral STN DBS | 22         | 16                      | 60.75 ± 2.1               | 9.8 ± 0.6                          | 1135.4 ± 91.4                         | 5.85 ± 1.15                     | 2.19                                 |
| Barichella et al. | 2003 | Prospective case study | bilateral STN DBS | 30         | 12                      | 60.0 ± 7.1                | 13.5 ± 3.7                          | 8314 ± 404.7                          | 9.3 ± 6.2                       | NA                                   |
| Escamilla-Sevilla et al. | 2011 | Prospective case-control study | bilateral STN DBS | 20         | 6                       | 58.0 ± 13.2               | 11.7 ± 3.9                          | 1470.5 ± 666.4                        | 3.6                             | 0.25                                 |
| Ford et al.     | 2004 | Prospective case study | bilateral STN DBS | 30         | 12                      | 58.8                     | 12.8                             | 1665                                 | 2.7                             | NA                                   |
| Foubert-Samier et al. | 2012 | Cross-sectional study between 1999–2006 | bilateral STN DBS | 47         | 55                      | 56.9 ± 8.1                | 12.6 ± 5.2                          | 1088.2 ± 354.9                        | 7.2 ± 8.1                       | NA                                   |
| Genty et al.    | 2011 | Prospective case study | bilateral STN DBS | 53         | 6                       | 59.9 ± 8.3                | 11.5 ± 4.2                          | 1138 ± 349                           | NA                             | NA                                   |
| Guimares et al. | 2009 | Prospective case study | bilateral STN DBS | 57         | 30                      | 61 ± 6.8                 | 14 ± 7.7                           | 1024.5 ± 431                         | 13.17 ± 10%                     | NA                                   |
| Jorgensen et al.| 2011 | Prospective case study | bilateral STN DBS | 10         | 12                      | 61.7 ± 6.5               | 13.3 ± 4.8                          | 878 ± 118                            | 4.7 ± 1.6                       | 1.76                                 |
| Lee et al.      | 2011 | Retrospective case-control study | bilateral STN DBS unilateral STN DBS | 25 18 | 24 18 | PD unilateral: 60 ± 2.5PD bilateral: 61.1 ± 1.1 | PD unilateral: 10.3 ± 0.92PD bilateral: 12.7 ± 1.4 | PD unilateral: 1245 ± 114 | 3.9 ± 2.0 (unilateral) | 5.6 ± 2.1 (bilateral) | NA |
| Limousin et al. | 1998 | Prospective case study | bilateral STN DBS | 24         | 12                      | 56 ± 8                   | 14 ± 5                             | 1224 ± 723                           | 4.2                             | NA                                   |
| Locke et al.    | 2011 | Retrospective case study | STN DBS (bilateral and unilateral)GPI - DBS (bilateral and unilateral) | 18 | NA | NA | NA | 4.29 ± 6.79 lb (Pounds) | NA |
| Macia et al.    | 2004 |                     | bilateral STN DBS | 19         | 12                      | 59.9 ± 6.60               | 15 ± 3.2                           | 993 ± 408                            | 9.7 ± 7.0                       | 0.8                                 |

(Continues)
| Reference       | Year  | Study type       | Stimulation Target | N enrolled | Mean follow-up (months) | Mean age at surgery (yrs) | Mean disease duration before surgery (yrs) | Mean preoperative levodopa dose (mg) | Mean increase of body mass (kg) | Mean effect size of body mass gain (Cohens’ d) |
|-----------------|-------|------------------|--------------------|------------|-------------------------|---------------------------|--------------------------------------------|----------------------------------|---------------------------------|----------------------------------|
| Markaki et al.  | 2012  | Prospective case study | bilateral STN DBS | 23         | 6                       | 65.2 ± 8.9                | 12.7 ± 6                                    | 998 ± 252                        | 3.09 ± 5.0                      | NA                               |
| Millan et al.   | 2017  | Prospective case study | bilateral STN DBS | 14         | 24                      | 60 ± 6.8                  | 2.2 ± 1.4                                  | NA                              | NA                              | NA                               |
| Mills et al.    | 2012  | Prospective case-control study | Bilateral STN DBS | 61         | 12                     | 61.5 ± 9.5                 | NA                                         | NA                              | NA                              | NA                               |
| Moghaddasi & Bosham | 2010 | Retrospective case study | bilateral STN DBS | 15         | 3                       | 51.8 ± 8.3                 | 8.5 ± 1.5                                  | NA                              | 3.4                             | 0.41                             |
| Montaurier et al.| 2007 | Prospective case-control study | bilateral STN DBS | 24         | 3                       | 61.51 ± 1.4                | 10.0 ± 1.05                               | 1174 ± 89                        | 3.4 ± 0.6                       | 0.16                             |
| Moro et al.     | 1999  | Prospective case study | bilateral STN DBS | 7          | 16                      | 57.4                      | 15.4                                       | 1507.3 ± 821.5                   | 7.9                             | 1.34                             |
| Novakova et al. | 2007  | Retrospective survey study | bilateral STN DBS | 25         | 45                      | 55.0                      | 15.0                                       | NA                              | 9.4                             | NA                               |
| Novakova et al. | 2011  | Prospective case study | bilateral STN DBS | 27         | 12                      | 56.8 ± 7.0                 | 12.5 ± 4.0                                | 1330 ± 538                       | 5.2 ± 5.8                       | 0.34                             |
| Ostergaard & Sunde | 2006 | Prospective case study | bilateral STN DBS | 33         | 48                      | 59 ± 8                     | NA                                         | 804 ± 364                       | 4.9                             | 0.30                             |
| Perlemoine et al.| 2005 | Prospective case-control study | bilateral STN DBS | 19         | 13                      | 59.9 ± 6.6 (SEM)           | NA                                         | 1336 ± 408 (SEM)                | 9.7                             | NA                               |
| Rieu et al.     | 2011  | Prospective case-control study | bilateral STN DBS | 22         | 12                      | 60.7 ± 1.5                 | 9.6 ± 0.9                                  | 868.5 ± 105.6                    | 8.4                             | NA                               |
| Romito et al.   | 2002  | Prospective case study | bilateral STN DBS | 22         | 23                      | 56.3 ± 7.7                 | 14.4 ± 5.9                                | 1505.9 ± 722.8                   | 8.1 ± 14.4                      | 0.57                             |
| Rouille et al.  | 2015  | Retrospective case-control study | bilateral STN DBS | 36         | 6                       | 60.3 ± 6.8                 | 12.6 ± 4.1                                | 1103.5 ± 341.5                  | NA                              | NA                               |
| Ruzicka et al.  | 2012  | Prospective case study | bilateral STN DBS | 20         | 18                      | 56.6 ± 5.8                 | 13.2 ± 4.5                                | NA                              | 6.9                             | 0.40                             |
| Reference      | Year  | Study type        | Stimulation Target | N enrolled | Mean follow-up (months) | Mean age at surgery (yrs) | Mean disease duration before surgery (yrs) | Mean preoperative levodopa dose (mg) | Mean increase of body mass (kg) | Mean effect size of body mass gain (Cohens' d) |
|---------------|-------|-------------------|--------------------|------------|-------------------------|---------------------------|------------------------------------------|---------------------------------|--------------------------------|----------------------------------|
| Ruzicka et al. | 2015  | Prospective case study | bilateral STN DBS  | 20         | 17                      | 56.6 ± 5.8                | 13.2 ± 4.5                                      | NA                             | 4.8                             | NA                               |
| Sauleau et al. | 2009  | Prospective case-control study | bilateral STN DBS bilateral GPi-DBS | 32         | 6                       | 57.7 ± 8.2                | 11.9 ± 3.9                                      | 1.337 ± 448                      | 5.7 ± 5.4                        | NA                               |
| Sauleau et al. | 2014  | Prospective case study | bilateral STN DBS  | 23         | 12                      | NA                       | NA                                        | 1.115 ± 529                      | 24.2 ± 5                         | NA                               |
| Schüpbach et al. | 2005 | Prospective case study | bilateral STN DBS  | 37         | 60                      | 54.9 ± 9.1                | 15.2 ± 5.3                                      | 1468 ± 811                       | NA                             | NA                               |
| Seifried et al. | 2013 | Prospective case study | bilateral STN DBS  | 11         | 6                       | 63 ± 7                    | 14 ± 4                                      | 1054.0                          | 5.1                             | 0.34                             |
| Serranova et al. | 2011 | Prospective case-control study | bilateral STN DBS  | 20         | NA                      | 58.3 ± 6                  | 15.7 ± 4                                      | 550.3 ± 479                      | 8.1                             | 0.64                             |
| Serranova et al. | 2013 | Retrospective case study | bilateral STN DBS  | 11         | NA                      | 56.3 ± 5                  | 14.4 ± 3                                      | 643.8 ± 459.0                    | 5.6                             | 0.45                             |
| Strowd et al. | 2016  | Retrospective case-control study | unilateral STN DBS bilateral STN DBS | 10         | 21                      | 66 ± 8.1                  | 10.3 ± 5.8                                      | 827 ± 495                       | 2.9 ± 9.4                        | NA                               |
| Tuite et al.  | 2005  | Retrospective case study | bilateral STN DBS  | 27         | 12                      | 64                        | NA                                        | NA                             | NA                             | NA                               |
| Walker et al.  | 2009  | Prospective case-control study | unilateral STN DBS  | 39         | 12                      | 59.1 ± 10.1               | 11.4 ± 6.1                                      | 1255.3 ± 611.7                   | 4.2 ± 7.3                        | 0.31                             |
We also evaluated the time course of BMI gain and found an increase of +1.00 kg/m² already 3 months after DBS (baseline BMI, 25.14; range BMI gain, +0.10–1.27 kg/m²; 95% CI, -1.29, -0.71; N = 185; p = .0042; d = 1.08; Figure 3). Here, the number of patients with overweight increased from 46% to 70%. The change in mean BMI from baseline to 6 months was +1.57 kg/m² (baseline BMI, 25.14; range BMI gain, 0.81–2.00 kg/m²; 95% CI, -1.92, -1.21; N = 236; p = .0004; d = 0.87) with an increase in the proportion of patients with overweight from 55% to 77%. At 12 months follow-up, BMI increased by +2.12 kg/m² (baseline BMI, 24.49; range BMI gain, 0.40–4.70 kg/m²; 95% CI, -3.33, -0.91; N = 199; p < .0001; d = 2.14). Thereby increased the proportion of patients with overweight from 52% at baseline to 88%. At a postoperative interval of greater than 12 months, the BMI increased by +1.97 kg/m² (baseline BMI, 23.9; range BMI gain, 0.87–2.90 kg/m²; 95% CI, -4.52, 0.58; N = 103, p = .0031; d = 1.65) compared to the preoperative BMI. In this subgroup, 100% had normal weight before surgery, of which 44% developed overweight.

3.5 Effects of STN DBS on motor function

In the 25 studies (N = 696) with complete UPDRS III datasets, the overall pooled mean UPDRS III in the
DBS ON state decreased from 34.7 (range 6.4 – 67.6) at baseline to 16.7 at the latest follow-up (range 5.0 – 39.3; 95% CI, 12.48, 23.53; p < .0001). Similarly, DBS led to an improvement of the mean dyskinesia score in the UPDRS IV from 4.87 (range 1.45 – 11.00) to 1.88 (range 0.15 – 2.55; 95% CI, 1.54, 4.43; N = 252; p = .0014) postoperatively.

3.6 | Change in LEDD

In 24 studies (N = 652), the overall pooled mean LEDD decreased from 1141 mg at baseline (range 831 mg – 1507 mg) by 56% to 644 mg at the latest available follow-up (range 402 mg – 1149 mg; 95% CI, 397.82, 596.44; N = 652; p < .0001). In keeping with other studies, our results thus confirm a clear improvement in motor function and a significant reduction in levodopa doses after stimulation.

3.7 | Predictors of weight gain following STN DBS

In search for predictive factors of body weight gain after surgery, we performed a correlation analysis of the following variables: delta weight, delta BMI, delta LEDD, delta UPDRS III, delta UPDRS IV, disease duration, age, as well as weight preoperatively. Change in weight was correlated with age (r = -0.4239, p = .031; Figure 4). Regarding the symptoms of PD, mean change in BMI was positively correlated with mean change in LEDD (r = 0.440, p = .0231) and with mean change in UPDRS III scores when ‘on L-Dopa’ (r = 0.502, p = .010; Figure 4). Postoperative mean change in LEDD was correlated with disease duration (r = -0.399, p = .022; Figure 4).

4 | DISCUSSION

The focus of this systematic review was to provide a comprehensive analysis of recently published studies that investigated body mass gain after STN DBS as a starting point for the development of new approaches to prevent this clinically relevant side effect. All but one study (50) reported weight gain after DBS with no study reporting weight loss. Thus, there is strong and consistent evidence for weight gain after STN DBS affecting the vast majority of patients.

The body weight gain occurs already in the first months after DBS implantation and appears to stabilize after one year. The maximum body mass gain across studies was 5.9 kg after one month and 11.1 kg one year after DBS. Nine studies investigated the body mass change 3 months after the surgery showing a mean increase in body weight of 3.25 kg. There was no detailed discussion about the exact mechanisms of this rapid weight gain in these articles. Interestingly, the Swedish Obese Subjects (SOS) study, which investigated the effects of bariatric surgery on subjects with obesity, found a mirrored effect. Here, subjects with obesity lost weight very rapidly during the first months after surgery followed by a plateau phase. There seem to be general mechanisms that may drive these rapid body weight changes after interventions. Further investigations are required to address these effects more precisely.

As our patient sample had normal weight prior to surgery, the body mass gain does not necessarily compensate for preoperative malnutrition or underweight which is well in line with recent evidence. In this context, it is also important to assess the changes in body composition after DBS-surgery. However, only a few studies reported in

FIGURE 4  Predictive factors of weight gain after STN DBS in patients with PD. (A) Correlation of postoperative change in weight and age. (B) Correlation of mean change in BMI and mean change in LEDD. (C) Correlation of mean change in BMI and mean change in UPDRS III scores. (D) Correlation of mean change in LEDD and Disease Duration. All values mean differences between pre- and postoperative values.
detail on changes in body composition. There is evidence that females gained disproportionately fat mass while weight gain in men was driven by both, fat free mass and fat mass.6,13,14,23,40,42,48,54

Interestingly, patients with a greater improvement of motor dysfunction and a stronger reduction in LEDD were likely to gain less weight arguing that an optimal lead localization in the sensorimotor part of the STN is associated with a lower likelihood to develop this side effect. This finding seems to be contractionary on the first view. On the one hand, DBS improves rigidity and rest tremor which would otherwise contribute to a higher preoperative energy expenditure that decreases postoperatively and leads to increased weight. On the other hand, patients perform larger movements and are more mobile than before the operation which should theoretically increase energy expenditure. In keeping, patients with a larger motor improvement and a stronger LEDD reduction were less likely to have an increased weight postoperatively. Although the weight gain is less pronounced in patients with an optimal lead positioning in the motor part of the subthalamic nucleus (STN), they may still gain weight despite reduction in resting energy expenditure. For future studies, it would thus be important to assess the mobility of a patient using quantitative measures, e.g. by wearable sensors and to measure both, resting- and activity-dependent energy expenditure. Moreover, mechanisms other than changes in energy expenditure that contribute to postoperative weight gain, e.g. changes in the hedonic control of food intake, should be taken into consideration. In the revised version of the manuscript, we adjusted the discussion and have tried to solve these seemingly contradictory finding.

However, the effect of body mass gain following DBS is not limited to patients with PD and to the STN as stimulation target. Body mass gain after surgery has also been observed in other movement disorders including dystonia and essential tremor (ET).8-10 Furthermore, body mass gain was reported in patients with PD treated with GPI DBS and unilateral pallidotomy.8,36,47,51,53 The body mass increase, however, was significantly higher in patients with PD and bilateral STN DBS in comparison to unilateral STN stimulation and bilateral GPI DBS.8,47,59 Similarly, patients with STN DBS gained more body mass than patients with stimulation in the GPI.8 Interestingly, VIM DBS resulted in no weight change in patients with ET, but in a significant body mass gain in patients with PD.50,20 These results collectively suggest that DBS may exert a general effect on physiological mechanisms of body mass homeostasis. It remains elusive to which extent the improvement of the underlying movement disorder is related to body mass changes. The target-dependent extent of body mass change may point towards to the involvement of different mechanisms that go beyond the pure normalization of abnormal movement patterns.

4.1 Impact of dopamine replacement therapy

The impact of dopamine replacement therapy on weight changes in patients with PD are only rarely studied and are still controversial. It has been shown that patients on levodopa significantly loose body weight within one year of treatment in comparison to patients on dopamine agonists.61 Here, the effect was dose-dependent: higher LEDD at baseline in levodopa-treated patients was associated with a more rapid weight loss.61 In contrast, other studies found no clear relationship between BM changes and LEDD although the results may depend on the type of medication.35 For example, ropinirole had no effect on BM, whereas cabergoline and pergolide led to unintentional weight loss, and pramipexole increased BM in patients with PD.25

Besides the role of dopamine in motivational and reward processing, catecholamines are also involved in the regulation of brown adipose tissue (BAT) thermogenesis. Recent evidence revealed that BAT-dependent non-shivering thermogenesis is involved in regulation of body weight and could increase insulin sensitivity.62 One possible suggestion is that dopamine replacement therapy may facilitate mitochondrial UCP1-induced thermogenesis, which could potentially also influence BM.

4.2 Physiological mechanisms

Body mass homeostasis is a complex and multifactorial process that is determined by physiological, metabolic, genetic, epigenetic, motivational, and behavioural factors.34,35 In PD, body mass is a non-motor feature and body mass changes are known to occur at all stages of the disease. Low body mass is often reported in the prodromal stage of PD and further decrease in body mass has been shown during disease progression.35 This process is associated with a continuous loss of fat mass. The body mass loss is associated with a variety of processes like difficulties with eating due to motor dexterity, decreased caloric intake, increased muscle rigidity, levodopa-induced dyskinesias, dysphagia, dysfunction of central energy homeostasis, increased metabolic demand due to motor symptoms, impaired olfaction and cognition, sarcopenia, as well as depression and an impact of dopaminergic medication.21,34,35,49,52

Body mass changes after DBS appear to have overlapping mechanisms with body mass loss in non-operated patients. In keeping with this notion, the observed DBS-related weight alterations involve changes in nutritional intake and eating behaviour, changes in energy expenditure, perturbations of homeostatic control, modulations by dopamine replacement therapy and dosage, changes in hormone- and neurotransmitter systems, as well as improvement in motor function as discussed in more detail below.31,34,35,41,52

4.3 Changes in motor function

A plausible mechanism for postoperative body weight gain is the amelioration of motor sign severity. The improved motor function, i.e. due to reduction of rigidity, dyskinesias, limb akinsesia, tremor and improvement of gait as well as reduction of dopaminergic medication collectively give rise to reduced energy expenditure.4,12,25-29,37,51 In contrast, other studies found no correlation between body mass gain and changes of the UPDRS III score.14,47,51 Taking advantage of our systematic approach however, we found less or no weight gain in patients with a higher improvement of disease severity. This
A compelling hypothesis is a reduced secretion of growth hormones with consequently decreased lipolysis. Furthermore, a drop of HDL cholesterol concentrations has been observed. Additionally, one study found an increased glucose oxidation after DBS implantation. These results remain contradictory as the basal glucose production and insulin sensitivity were reported to be unchanged in a different study. To sum up, there is first evidence that STN DBS affects glucose and lipid metabolism, but this is still contrarily discussed.

4.5 Changes of brain function

Recent PET studies using 2-deoxy-2[18F]fluoro-D-glucose tracer found a correlation between STN DBS-related weight gain and metabolic changes in associative and limbic brain areas, but no correlation with sensorimotor brain regions. These findings suggest that the STN might be involved in motivational processing related to eating behaviour. Indeed, the STN is connected to the limbic system, especially to the ventral tegmental area and ventral pallidum, which are key structures of the reward system. Through its connections, stimulation of the STN may thus increase dopaminergic conveyance in the striatum. Additionally, the medial part of the STN is adjacent to the medial forebrain bundle which contains essential projections underlying reward functions. Animal studies have shown that STN lesions and DBS led to increased food-related incentive motivation in rats but not to increased hunger. Moreover, an electrophysiological study in monkeys revealed an increased firing rate of neurons in the STN related to the delivery of rewards. Therefore, an active electrode in the vicinity of the medial STN may influence food-related reward processing resulting in changes of motivational behaviours, food intake, and body weight. Body mass gain thus could result from increased sensitivity to food reward cues and changes in eating behaviour, including higher food intake, increased appetite, binge eating, or craving.

4.6 Hypothalamic alterations in adipokine release

Patients with PD and STN DBS showed increased levels of the orexigenic neuropeptide Y (NPY) after DBS implantation. The increased NPY levels correlated with a higher stimulation amplitude which could indicate that DBS may disrupt the melanocortin system by electric current diffusion to the hypothalamus. Interestingly, the central hormone NPY exerts effects on food intake and body weight using different mechanisms including a relationship to the actions of glucocorticoids. Moreover, rodent models showed that neuropeptide Y levels are altered in neurodegenerative disorders like PD or Alzheimer's disease. Furthermore, leptin and ghrelin as peripheral hormones are involved in the regulation of energy balance. Leptin is a long-term mediator for energy balance, whereas ghrelin is a fast-acting hormone for meal initiation. Both systems are disturbed in obesity and are therefore important to consider in the context of weight gain after DBS surgery. It has been shown that DBS is accompanied
with increased serum leptin levels, reflecting an increased degree of adipose tissue. In addition, increased levels of ghrelin after STN DBS was likewise reported and could lead to an resistance to the anorexi- genic effect of leptin within the hypothalamus.\(^{13,23,33,41,42,65,73}\) Also reduced growth hormone secretion has been described after STN DBS,\(^{74,75}\) which results in decreased lipolysis and thus to body mass gain.

One assumption for these endocrine alterations is that the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of hormone secretion, energy homeosta-

Moreover, it has been shown that cortisol levels are normalized after STN DBS and the respective anabolic effect of this normalization process has been hypothesized to drive the body mass gain.\(^{23,42,54,76}\) In addition, it has been shown that cortisol levels decreased over time after DBS\(^{23,55}\) and that this decrease was correlated with the position of the active electrode in the STN. The more medially the electrode was located, the greater was the decrease in cortisol levels. Furthermore, lower cortisol levels were strongly associated with weight gain and higher trait anxiety.

These results seem to be contractionary to the relationship between cortisol levels and body mass gain with patients with abdomi-

Thus, we were not able to generate forest and funnel plots due to missing data. Given that only six studies included sufficient information about control groups, it was not possible to calculate the necessary odds ratios.

Further limitations are the limited range of clinical disease severity due to guidelines for the treatment with DBS and the impossibility to randomize groups. Some reports found no change in food intake, appetite, or hunger which could be due to the fact of inaccuracy of self-reported intake.\(^{33}\) In addition, most studies covered only a limited time period (in most cases 12 months). Longer assessment periods are warranted to investigate the complete time course of body mass changes.

5 | CONCLUSIONS

Deep brain stimulation is an efficacious technique that greatly improves motor and non-motor symptoms and the quality of life of patients with PD. Our results, however, suggest that body mass gain is one of the most common side effects of DBS. Body mass gain occurs rapidly and persistently in almost all patients. Postoperative body mass gain is a multifactorial phenomenon and can have negative health implications. Some patients with PD might develop postoperative obesity and related insulin resistance, and in the long-term diabetes and cardiovascular diseases.

Therefore, the clinical implications from our results is that all patients should be informed that weight gain may occur as a consequence of DBS. Potential candidates for this treatment may be given preoperative nutritional counseling, physiotherapy, and sports therapy after the implantation to prevent rapid weight gain leading to obesity. Moreover, larger and better controlled trials are needed to establish long-term efficacy of nutritional intervention studies.

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CONFLICTS OF INTEREST

No conflict of interest was declared.

AUTHOR’S CONTRIBUTION

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

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