REVIEW

# Apathy Induced by Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Meta-Analysis

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**ABSTRACT:** Apathy, the loss of motivation, is a common problem in Parkinson's disease (PD) and often observed following deep brain stimulation (DBS) of the subthalamic nucleus (STN). The aim of this meta-analysis was to determine the occurrence of apathy following STN DBS in literature. Relevant articles were searched in PubMed/Medline, SCOPUS, EMBASE, and Web of Sciences electronic databases. Studies were included if they reported apathy scores pre- and post-DBS or the cross-sectional difference between PD patients receiving STN DBS and patients receiving medication only. Thirty-three articles were included in the meta-analyses from 6,658 screened articles by two authors independently. A total of 1,286 patients were included with a mean age (±standard deviation [SD]) of 58.4 ± 8.5 years and a disease duration of 11.0 ± 5.8 years. The apathy score measured by means of the Apathy Evaluation Scale (AES), Starkstein Apathy Scale (SAS), and the Lille Apathy Rating Scale (LARS) was significantly higher after DBS than pre-operatively (g = 0.34, 95% confidence interval [CI] = 0.19–0.48, $P < 0.001$). An equal, significant difference in severity of apathy was found between STN DBS and medication only (g = 0.36, 95% CI = 0.03–0.65; $P = 0.004$). Statistical heterogeneity was moderately high, but the effects stood strong after multiple analyses and were independent of tapering off dopaminergic medication. The findings of this meta-analysis indicate that apathy is increased after STN DBS compared to the pre-operative state and to medication only (systematic review registration number: PROSPERO CRD42019133932). © 2020 Universiteit van Amsterdam. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

**Key Words:** apathy; Parkinson; deep brain stimulation; subthalamic nucleus

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity, and rest tremor.[1] Of PD patients, 60%–90% will develop non-motor symptoms such as cognitive decline, anxiety, and depression.[2] Although dopaminergic drugs treat the motor manifestations effectively, they may be accompanied by side-effects such as response fluctuations, dyskinesias, and impulse control disorders.[3] Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the globus pallidus internus (GPi) are effective treatments for PD.[4-6] As a result of motor improvement after STN DBS, dopaminergic medication can usually be reduced.[7]

Apathy is an increasingly recognized non-motor manifestation of PD, commonly described as loss of motivation, decreased initiative, interest, and energy, and an emotional indifference with flattened affect.[2,8] Apathy has received more interest in recent years and validated clinical diagnostic criteria have been published.[9]



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Furthermore, apathy is frequently measured in studies in PD and has a high impact on quality of life (QoL).[10,11] Contrary to most non-motor symptoms, apathy may worsen after STN DBS in up to 71% of cases.[10,12-15] The results of the meta-analysis by Wang et al[16] were among the same lines. However, this meta-analysis had methodological limitations, including the narrow search strategy, the use of the fixed effects model, and the inclusion of studies with overlapping samples.[17,18]

Possible causes for increased apathy are reduced dopaminergic stimulation after medication reduction following STN DBS or collateral stimulation of adjacent regions to the motor territory of the STN.[19-21]

We performed a systematic review and meta-analysis to test the hypothesis that apathy increases in PD patients treated with STN DBS compared to either a pre-operative state or to a control group by including newer and larger trials.

## Methods

The systematic review and meta-analysis were designed according to the PRISMA Guidelines.[22] A clinical librarian (J.D.) developed the search strategy for the meta-analysis (Supplementary Appendix S1).

### Search

The search included studies that published apathy scores in PD patients with STN DBS in a longitudinal or cross-sectional design, were written in English, reported apathy scores in original data or this information could be reconstructed, and used one of the apathy scales that were recommended by the International Parkinson and Movement Disorders Society (MDS) — ie, Apathy Evaluation Scale (AES), Starkstein Apathy Scale (SAS), Lille Apathy Rating Scale (LARS), and the Apathy Inventory (AI).[23-27]

Studies were excluded if the results consisted of non-original research, less than six patients were reported, the study was part of an intervention trial for apathy and the last assessment of apathy took place earlier than 2 weeks post-operative. Additionally, studies with a cross-sectional design were excluded if the study had no control group consisting of PD patients treated with medication alone. We chose 2 weeks post-operatively as the lower threshold for assessing apathy. Hereby, we were able to analyze whether STN-DBS has an effect on the apathy scores over time.

Relevant published articles were searched in PubMed/Medline, SCOPUS, EMBASE, and Web of Sciences electronic databases. The electronic databases were searched up to September 4th, 2020 in three separate subsets, one on PD and STN DBS, one on PD and apathy, and the third on PD, STN DBS, and apathy. The titles and abstracts were independently screened by two authors (T.Z. and G.B.) for inclusion in full-text appraisal. Similarly, these two authors independently appraised the full texts of these studies after excluding duplicate articles. Discrepancies were resolved through discussion and when consensus could not be achieved, a third author (GvR) would have the final decision on the inclusion in the meta-analyses and systematic review.

### Data Collection Process

The screening authors extracted the data and discussed accuracy routinely throughout the extraction phase. Authors were contacted when studies lacked sufficient methodological information or to provide additional data. When the screening process revealed multiple publications on the same data set, the study with the largest number of participants was used.

The following variables were collected from the included studies: authors, publication date, study design, total number of participants, population characteristics (ie, age, sex, disease duration), months of follow-up, whether apathy was the primary outcome, apathy scale, apathy scores, depression scores, anxiety scores, QoL scores, levodopa (L-dopa) equivalent daily dosage (LEDD), cognitive tests, unilateral or bilateral stimulation, Unified Parkinson Disease Rating Scale (UPDRS), and the MDS-UPDRS.[28,29] The quality of articles was assessed using the adapted Newcastle Ottawa Scale (NOS) for observational studies (range 0–8).[30] A NOS score of five or less is indicative for a high risk of bias.

### Meta-Analysis

We performed three separate meta-analyses using a DerSimonian and Laird random-effects model: one pooling longitudinal data (change in apathy score from before to after STN DBS), one pooling cross-sectional data (difference between a post-operative STN DBS group with a control group), and one pooling cross-sectional longitudinal data (pre-post change scores of a STN DBS group compared with pre-post change scores of a control group).[29,31-36] Studies with longitudinal and cross-sectional apathy scores were included in all meta-analyses. Case control studies with only longitudinal data were categorized as longitudinal studies. In longitudinal studies with multiple recordings of apathy, the closest measurement to 6 months post-operative was used because the incidence of DBS-related apathy is thought to be highest in the early months after STN DBS.[15] The principal summary measure for each meta-analysis was an effect size expressed as Hedges g with a statistical significance level derived from the mean and standard deviation (SD) or *F* scores. If the mean, SDs, and *F* scores were unavailable, the mean and SDs were reconstructed by simple statistics in the case of normally distributed data.[37-40] All statistical analyses were performed using R with packages "meta" and "metafor."[41]

Small study effects or publication bias were assessed using the funnel plot test and Egger's statistics and a trim-and-fill analysis was performed when the Egger's test was positive.

The heterogeneity between studies was quantified by the index of heterogeneity ($I^2$). A $P$ value of <0.05 was considered as evidence of heterogeneity. Meta-regressions were carried out on common variables such as the exclusion of patients suffering from apathy, depression, and/or other neuropsychiatric illnesses apathy based on clinical evaluation or the cut-off of the appropriate scale at baseline. Subgroup analyses were performed on the study design, different scales, UPDRS, LEDD, disease duration, and age as grouping variables for their relation to apathy.

# Results

## Study Selection

The flow chart of the study selection process is presented in Figure 1. The search yielded a total of 6,658 articles and 1,319 of these were considered eligible. Subsequently, 1,263 studies were excluded because of lack of a validated apathy scale or inappropriate interventions and control groups. Authors were contacted with a high response rate of 82.4% to identify studies with overlapping data sets or to provide additional information, after which 23 additional studies were excluded and 33 remained, 23 with a longitudinal design and 13 with a cross-sectional design. Three studies had both a longitudinal and cross-sectional design, and these studies were also combined in a separate meta-analysis.[42-44]

## Study Characteristics

A total of 1,286 PD patients were included with a mean age (±SD) of 58.4 ± 8.5 years and a mean disease duration of 11.0 ± 5.8 years. Study characteristics of the longitudinal and cross-sectional studies are presented in Tables 1 and 2, respectively. The AES was used in 10 studies, the SAS in 22 studies, and the LARS in three studies.[23] For uniformity, the SAS was prioritized for analyses if studies reported two scales.[46,47] The mean apathy scores at baseline were: SAS 5.4 to 18.8, AES 27.5 to 39.1, and LARS −32.6 to −24.0.[13,56] For

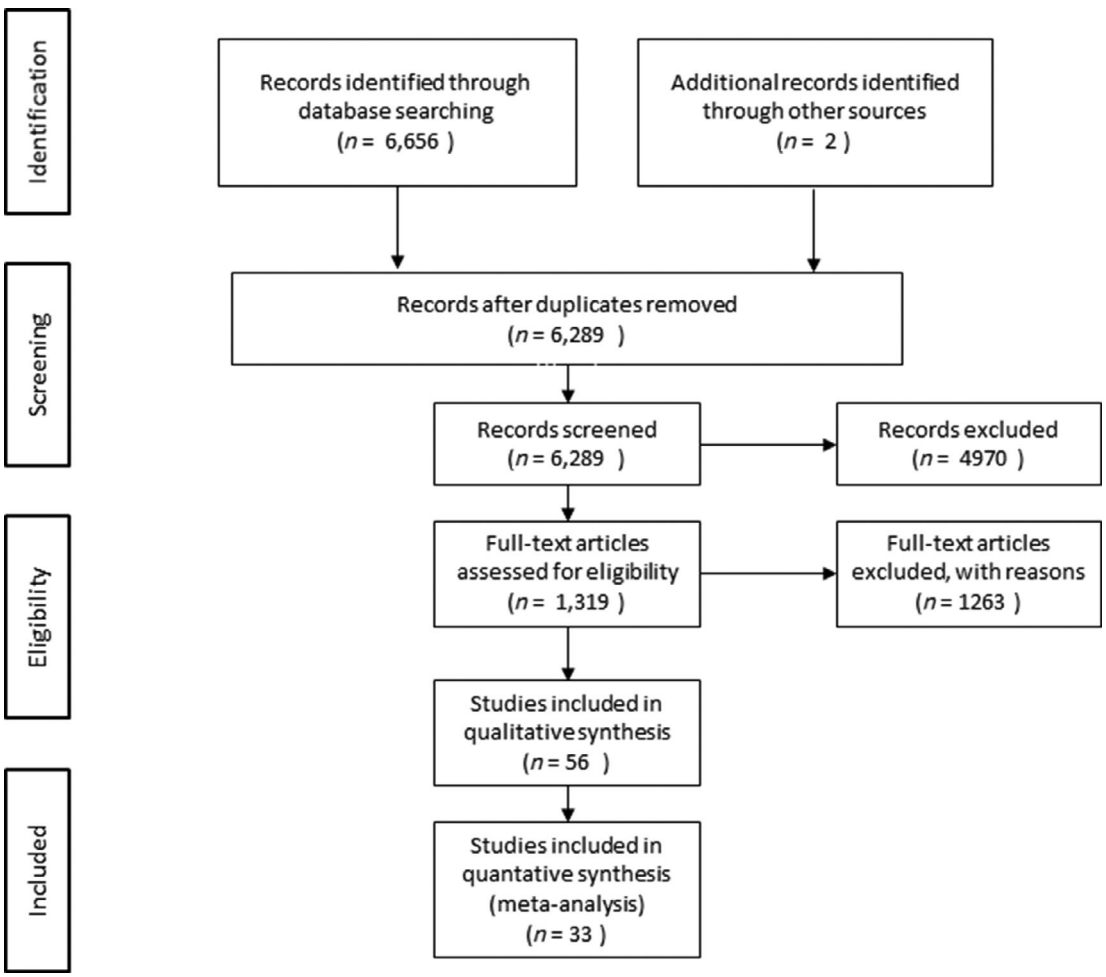


**FIG. 1.** Flow diagram of study selection.

**TABLE 1.** Longitudinal studies characteristics

| Study | Total sample | Age (y) | Disease duration (y) | Follow-up (mo) | Newcastle-Ottawa score | Apathy scale | Pre-operative score | Post-operative score | Mean change in LEDD (%) |
|---|---|---|---|---|---|---|---|---|---|
| Ardouin et al[44] | 7 | 54.0 ± 9.0 | NR | 3 | 7 | SAS | 9.5 ± 3.0 | 9.8 ± 6.3 | −73.6 |
| Castelli et al[45] | 19 | 62.1 ± 4.2 | 14.7 ± 5 | 17 | 7 | SAS | 11.6 ± 4.1 | 12.6 ± 5.3 | −52.1 |
| Castrioto et al[46] | 36 | 56.8 ± 8.3 | 9.3 ± 4.9 | 12 | 5 | SAS | 11.1 ± 4.8 | 10.4 ± 5.3 | −60.3 |
| Chou et al[47] | 10 | 62.1 ± 6.5 | 9.1 ± 5.8 | 6 | 7 | SAS | 13.2 ± 8.6 | 13.6 ± 7.4 | −51.2 |
| Dafsari et al[48] | 36 | 62.8 ± 9.1 | 9.6 ± 5.3 | 5 | 4 | AES | 28.9 ± 7.1 | 29.6 ± 6.7 | −53.3 |
| Dos Santos et al[49] | 19 | 60(6.5) | 93(3.5) | 12 | 7 | SAS | 6.9 ± 2.7 | 9.5 ± 7.7 | −39.6 |
| Drapier et al[43] | 30 | 59.7 ± 7.6 | 12.2 ± 2.8 | 6 | 7 | SAS & AES | 13.0 ± 6.5 | 18.8 ± 9.7 | −22.2 |
| Foley et al[50] | 28 | 57.5 ± 7.3 | 18.8 ± 6.1 | 19.5 | 6 | SAS | 10.8 ± 6.0 | 14.0 ± 11.2 | NR |
| Gesquiere-Dando et al[51] | 34 | 62.7 ± 8.1 | 9.9 ± 4.3 | 12 | 6 | LARS | −32.6 ± 3.6 | −24.4 ± 12.0 | −39.4 |
| Higuchi et al[13] | 25 | 50.4 ± 9.8 | 12.5 ± 7 | 1 | 7 | SAS | 5.4 ± 3.1 | 9.6 ± 9.9 | −61.1 |
| Langner-Lemercier et al[52] | 40 | 56.5 ± 7.8 | 12.0 ± 4.6 | 12 | 5 | AES | 30.9 ± 6.3 | 33.0 ± 8.9 | −38.9 |
| Le Jeune et al[53] | 12 | 57.4 ± 8 | 11.2 ± 2.4 | 3 | 6 | AES | 30.9 ± 4.1 | 39.1 ± 6.1 | −33.6 |
| Lhommee et al[54] | 73 | 57.3 ± 7 | 10.8 ± 2.9 | 12 | 7 | SAS | 6.4 ± 3.3 | 9.7 ± 4.6 | −69.7 |
| Lhommee et al[41] | 251 | 52.5 ± 6.3 | 7.5 ± 2.9 | 24 | 8 | SAS | 9.9 (0.7) | 12.7 (0.5) | −37.6 |
| Lilleeng et al[55] | 16 | 60.0 ± 8.1 | 12.9 ± 5.7 | 4.5 | 8 | SAS | 14.7 ± 4.1 | 16.9 ± 5.2 | −22.9 |
| Maier et al[56] | 30 | 61.2 ± 8.7 | 12.0 ± 6.79 | 3 | 7 | AES | 34.8 ± 10.9 | 34.6 ± 9.4 | −55.9 |
| Mosley et al[57a] | 64 | 62.2 ± 9.5 | 9.0 ± 5.2 | 1.5 | 7 | SAS | F-score: 0.838 | | NR |
| Nimura et al[58] | 39 | 62.6 ± 6.7 | 13.3 ± 9.4 | 6 | 5 | SAS | 12.2 ± 7.7 | 12.0 ± 7.2 | NR |
| Pham et al[59] | 40 | 63.4 ± 6.4 | 12.1 ± 3.8 | 3 | 6 | AES | 30.6 ± 5.9 | 32.2 ± 6.6 | −47.7 |
| Robert et al[17] | 44 | 56.3 ± 7.5 | 11.4 ± 4.1 | 3 | 6 | AES | 31.4 ± 6.4 | 31.6 ± 7.1 | −30.5 |
| Seifried et al[60] | 11 | 63.0 ± 7 | 14.0 ± 4 | 6 | 4 | SAS | 10.8 ± 7.1 | 12.5 ± 8.6 | −51.5 |
| Valldeoriola et al[42] | 23 | 57.9 ± 4.8 | 13.7 | 6 | 5 | LARS | −24 ± 19.9 | −27 ± 21.6 | −21.4 |
| Voruz et al[61] | 29 | 56.5 ± 8.0 | 11.2 ± 4.2 | 3 | 6 | AES | 31.4 ± 6.5 | 32.9 ± 8.7 | −44.0 |

Follow-up, apathy assessment follow-up in months after the STN DBS operation. All studies used bilateral stimulation. Studies with the variance marked as ± reported standard devations, studies with parentheses reported the standard error. Abbreviations: LEDD, levodopa equivalent daily dosage; SAS, Starkstein Apathy Scale; AES, Apathy Evaluation Scale; LARS, Lille Apathy Rating Scale; NR, not reported.
[a]*F* statistic was provided only.

uniformity, the SAS was prioritized for analyses in studies that reported two scales.[44,67] The risk of bias was high (NOS score ≤5) in 8 studies (24.4%) and low (NOS score >5) in 25 studies (75.8%). Two studies had a unique design; one with a L-dopa/carbidopa intestinal gel control group and one investigated effects of unilateral STN-DBS.[43,72]

## Synthesis of Results

The forest plots of the meta-analyses of the longitudinal studies are shown in Figure 2. A significant higher apathy score is found post-operatively than before DBS treatment (g = 0.34, 95% confidence interval [CI] = 0.19–0.48, $P < 0.001$, $I^2$ = 34%). Studies that

**TABLE 2.** Cross-sectional studies characteristics

| Study | Total sample | Age | Disease duration | Months post-operative | Newcastle-Ottawa score | Apathy scale | Score STN DBS group | Score control group | LEDD difference (%) |
|---|---|---|---|---|---|---|---|---|---|
| Crespo-Burillo et al[62] | 22 | 65.4 ± 7.7 | 21.2 ± 13.1 | 3 | 6 | SAS | 11.6 ± 7.1 | 11.4 ± 5.5 | NR |
| Czernecki et al[63] | 41 | 57.8 ± 1.8 | 13.9 ± 1.6 | 10 | 8 | SAS | 11.2(0.9) | 11.0(1.5) | −86.4 |
| Drapier et al[43] | 30 | 59.7 ± 7.6 | 12.2 ± 2.8 | 6 | 7 | SAS & AES | 18.8 ± 9.7 | 13.0 ± 6.5 | −22.2 |
| Enrici et al[64] | 38 | 60.3 ± 7.6 | 12.0 ± 6.8 | NR | 6 | SAS | 11.9 ± 3.6 | 12.8 ± 5.6 | −29.2 |
| Evens et al[65] | 66 | 65.5 ± 7.3 | 11.3 ± 6.2 | 3 | 6 | SAS | 15.5 ± 6.4 | 8.9 ± 4.7 | +6.3 |
| Hindle Fisher et al[66] | 60 | 66.3 ± 3.1 | 10.3 | 6 | 8 | SAS & LARS | 13.8 ± 4.7 | 12.1 ± 6.3 | −15.1 |
| Houvenaghel et al[67] | 50 | 57.8 ± 7.7 | 12.2 ± 3.3 | 30 | 5 | AES | 30.3 ± 8.8 | 27.5 ± 6.7 | −30.2 |
| Kojovic et al[68] | 20 | 59.3 | 9.4 ± 5 | NR | 5 | AES | 38.5 ± 2.2 | 32.2 ± 2.8 | −18.6 |
| Leimbach et al[69] | 24 | 63.6 ± 11.3 | NR | 3 | 8 | SAS | 15.0 ± 5.5 | 10.5 ± 5.3 | NR |
| Lhommee et al[41] | 251 | 52.5 ± 6.3 | 7.5 ± 2.9 | 24 | 8 | SAS | 12.7(0.5) | 11.4(0.5) | −48.2 |
| Mcdonald et al[70] | 34 | 57.4 ± 6.5 | 13.5 ± 5.2 | 14.5 | 8 | SAS | 13.0 ± 11.6 | 10.3 ± 6.4 | −12.6 |
| Okun et al[71a] | 30 | 59 ± 8.6 | 11.8 ± 3.9 | 6 | 8 | SAS | 16.4 ± 9.3 | 13.1 ± 6.0 | −17.2 |
| Valldeoriola et al[42] | 23 | 57.9 ± 4.8 | 13.7 | 6 | 5 | LARS | −27 ± 21.6 | −9 ± 15.8 | −21.4 |

Follow-up, apathy assessment follow-up in months after the STN DBS operation. Studies with the variance marked as ± reported standard deviations, studies with brackets () reported the standard error. Abbreviations: LEDD, levodopa equivalent daily dosage; SAS, Starkstein Apathy Scale; AES, Apathy Evaluation Scale; LARS, Lille Apathy Rating Scale; NR, not reported.
[a]One study used unilateral stimulation, all other studies used bilateral stimulation.

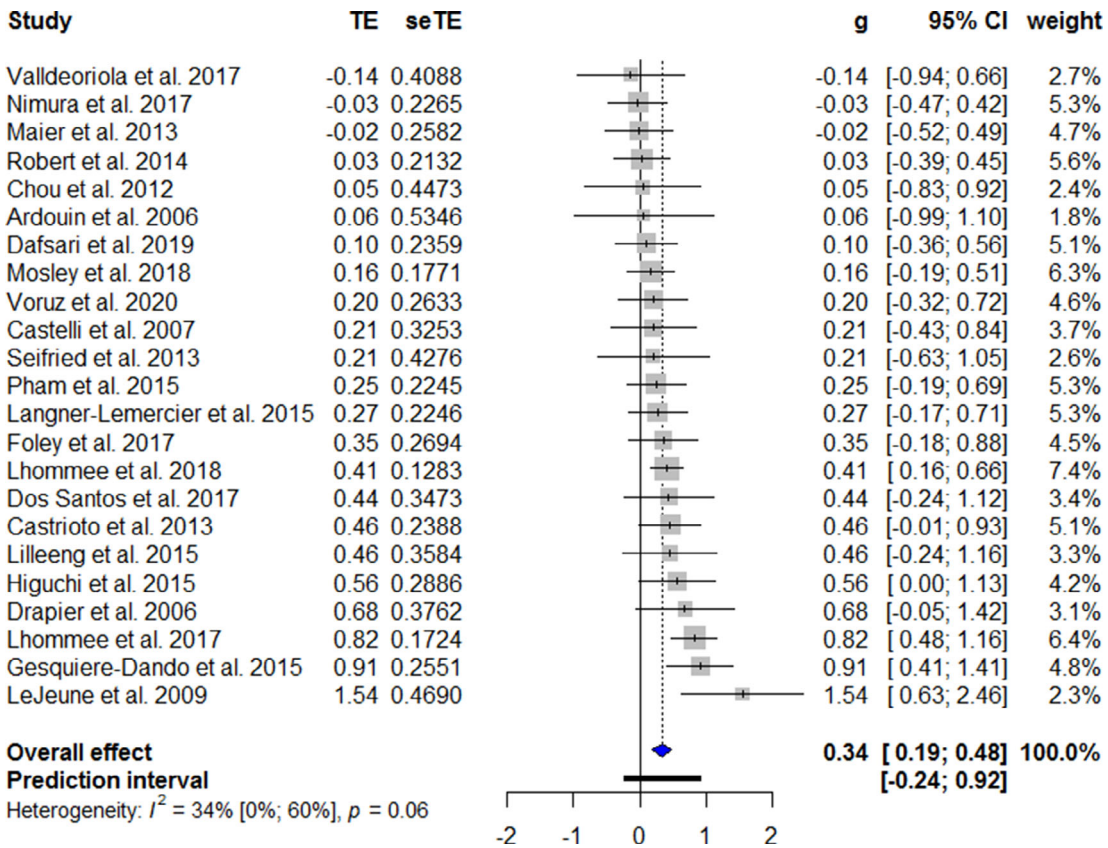


**FIG. 2.** Forest plot of apathy after STN DBS in longitudinal studies. Treatment effects to the right favors more apathy. TE, treatment effect; seTE, standard error of the treatment effect; g, Hedges' g; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

excluded patients with apathy at baseline found greater values of apathy after STN DBS (g = 0.79, $P < 0.001$). Studies that reported apathy as a main outcome also reported a higher mean apathy score following STN DBS (g = 0.46, $P < 0.001$). A higher pre-operative UPDRS III on-medication score ($F = 6.32$, $P = 0.03$) and a higher pre-operative Beck depression inventory (BDI) score ($F = 7.29$, $P = 0.04$) are associated with higher apathy scores after STN DBS. The follow-up UPDRS III on-medication score and BDI score were not associated with apathy outcomes. The meta-analysis for cross-sectional studies showed a similar difference in apathy (g = 0.36, 95% CI = 0.03–0.65; $P = 0.004$, I^2 = 58%). Please see Figure 3 for the respective forest plot. The heterogeneity could be improved by excluding the two studies with the unique designs (I^2 = 42.8%).[43,72] If the studies that did not report apathy as the main outcome were analyzed separately, there was no statistically significant effect (g = 0.31, $P = 0.25$). The forest plots of the three studies that had pre- and post-operative apathy assessments in both an STN DBS and a control group are shown in Figure 4. The combined studies did not demonstrate a statistically significant difference in apathy between the two treatment arms (g = 0.20, 95% CI = −0.27–0.67, $P = 0.40$).

### Additional Analyses

The Egger's tests provided no evidence for publication bias and there was no small effects bias (Fig. 5A, B). Using meta-regression, there were no relations between effect size and LEDD reduction ($P = 0.96$ for longitudinal; $P = 0.23$ for the cross-sectional studies), disease duration, and age on the overall effect in all meta-analyses. The mean increase of apathy score after STN-DBS on the SAS and AES were +2.03 for the longitudinal studies and +2.96 for the cross-sectional studies.

## Discussion

The main purpose of this systematic review and meta-analysis was to determine whether STN DBS resulted in higher apathy scores in PD patients. The main result of our meta-analysis is that apathy scores are higher after STN DBS for PD compared with the pre-operative state and compared with PD patients on medication alone. This result is relevant for clinical care to allow for careful consideration of the benefits and drawbacks of STN DBS for PD patients. Interestingly, increase in apathy appeared to be present regardless of

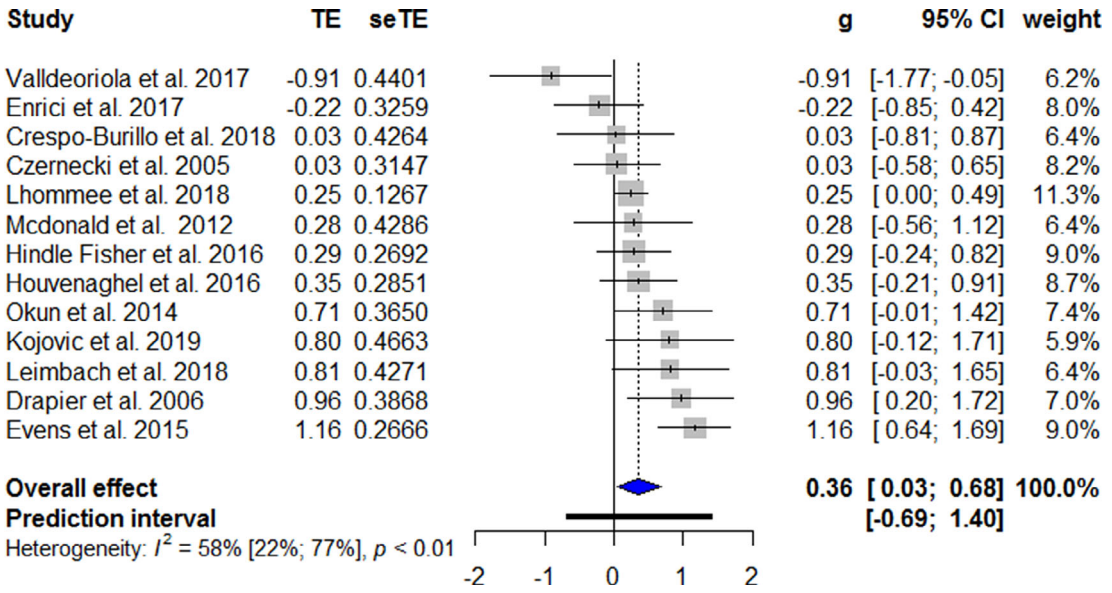


**FIG. 3.** Forest plot of apathy after STN DBS in cross-sectional studies. Treatment effects to the right favors more apathy. TE, treatment effect; seTE, standard error of the treatment effect; g, Hedges' g; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

reduction of dopaminergic medication, disease progression, and other neuropsychiatric symptoms.

The overall effect was roughly the same for longitudinal studies and cross-sectional studies. The smaller sample size in the cross-sectional meta-analysis led to more confounding variables than the longitudinal meta-analysis. We found no evidence that coincidence findings would be more often reported because of the absence of small-study effects. Studies that listed apathy as a main outcome had higher apathy scores than studies that did not primarily focus on non-motor symptoms, a possible explanation could be a more thorough examination of apathy symptoms. Furthermore, studies that excluded apathetic patients at baseline reported a higher difference in apathy scores between the pre- and post-operative assessment. This finding suggests that there may be a ceiling effect where already apathetic patients do not experience the same increase in symptom severity. A possible explanation is that apathy is related to PD severity and the decrease of dopaminergic medication, allowed by the effect of DBS, returns the apathy severity towards an untreated state. This is supported by the association between apathy and the pre-operative UPDRS on-medication score, a marker for dopaminergic unresponsive symptoms.

The difference in the severity of apathy between the STN DBS and best medical treatment groups was highest in studies with a follow-up shorter than 2 years. With longer follow-up, apathy increased also in the best medical treatment group and the difference in apathy between the groups decreased.[19] The SAS and AES showed some divergence in scores although scales have mostly overlapping questions and are possibly interchangeable in clinical use. Numerous studies also reported the Non-Motor Symptoms Scale and the Non-Motor Symptoms Questionnaire or UPDRS item 4.[73-75] Although these scales showed a correlation with apathy and have sub-scores related to apathy, they lack the specificity of the scales listed by the MDS for the assessment of apathy.[23]

The pathophysiology of apathy occurring in patients that are treated with STN-DBS is still under debate.

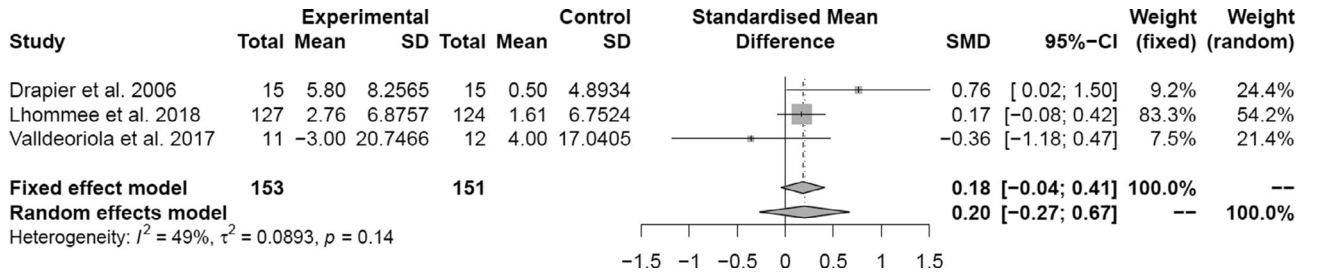


**FIG. 4.** Forest plot longitudinal and cross-sectional studies. Treatment effects to the right favors more apathy. SMD, standardized mean difference; CI, confidence interval.

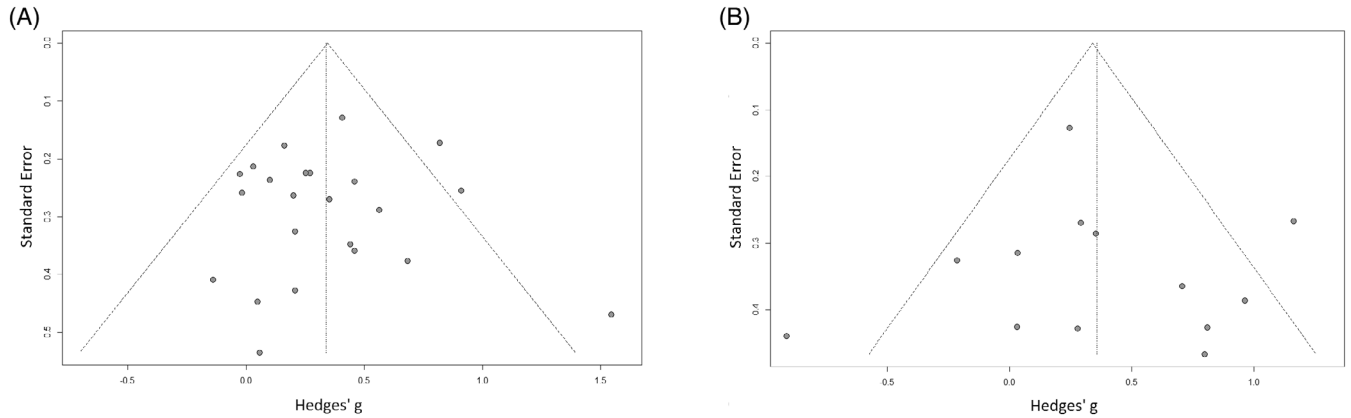


**FIG. 5.** (**A**) Funnel plot of the longitudinal studies. (**B**) Funnel plot of the cross-sectional studies.

The most notable hypotheses are that apathy increases with longer disease duration, reduction of dopaminergic medication, and DBS of areas adjacent to the motor subregions of STN or spillover of current into these areas.[10,14,19] The literature regarding the direct effects of DBS-current on apathy is inconsistent; some studies found an increase of apathy,[14,15,54] whereas others found that euphoria increases and apathy is reduced.[64,76]

Interestingly, the only randomized controlled trial directly assessing apathy—the EARLYSTIM-trial—did not detect a difference in apathy scores between the STN DBS and best medical treatment group. In the EARLYSTIM-trial, both the STN DBS and best medical treatment group had an increase of apathy scores during follow-up.[42] The dopaminergic medication is generally reduced in the weeks following STN DBS surgery. The reduced availability of mesolimbic and mesocortical dopamine accompanying the postoperative reduction in the use of dopaminergic medication is commonly theorized as the main contributing factor for apathy.[15,77,78] However, our meta-analysis revealed no effect from dopaminergic medication reduction on apathy scores on a group level. Three articles separated dopamine agonists use from other medications and these studies suggest that higher daily doses of dopamine agonists, which have a higher affinity to the limbic D3 dopamine receptor, are accompanied by lower apathy scores.[53,55,66,78]

Another factor for the development of non-motor features and apathy could be the severity of PD. Although the UPDRS on-medication score at baseline was associated with the occurrence of apathy, neither disease duration nor UPDRS III off-medication score were associated with the increase in apathy. The effect of DBS on apathy scores and level of statistical significance does not change when correcting for UPDRS on-medication score.

Furthermore, cognitive decline is also prominent in advanced PD because of age related illnesses (eg, Alzheimer's disease and cerebrovascular disease) and PD dementia.[79,80] However, literature is biased as surgical candidates are selected for absence of dementia. Moreover, most studies only used basic cognitive testing with screening instruments at a single point during the trials. As such, no relationship was found between apathy and neurocognitive functioning in our meta-analysis. This meta-analysis was also unable to establish a relationship between apathy and depression, anxiety, quality of life, social support, and other variables as the data on these factors was scarce and most studies did not report subscales.

This meta-analysis succeeded the meta-analysis of Wang et al[16] that concluded that apathy was more prevalent after STN DBS. Our meta-analysis was able to address some of the limitations of the earlier meta-analysis, added extra articles and the random effects demonstrates with a higher degree of confidence that our findings are relevant for the general PD population. Nevertheless, Wang et al[16] found an effect size of the same order as the effect sizes in our meta-analyses.

Our study had some limitations that need to be acknowledged. First, the heterogeneity of the studies was high in the longitudinal and the cross-sectional meta-analysis and the combined meta-analysis showed a divergence of the results. This reflects the different methodological procedures that were followed in the included studies and limits the reliability of our results. Subgroup analysis were performed and studies with a high impact on the heterogeneity were excluded, resulting in a higher overall effect remaining statistically significant. Second, we calculated the apathy scores in some studies by the estimation of a weighted mean and SD, without having access to the original data. Although these variables are less precise, we argue that the inclusion of these studies strengthened our meta-analysis. Third, several studies were at risk of bias based on the NOS. Sensitivity of these studies did not detect any outliers and the influence on the overall effect was not distinct from other studies. Fourth, we

included the closest apathy measurement point to 6 months post-operatively in both meta-analyses. The STN-DBS treatment may not be optimal at that time because of suboptimal electrode settings and medication adjustments. Fifth, an important finding is the lack of relation between reduction of dopaminergic treatment and apathy at group level. It would have been informative to relate LEDD-reduction with patients scoring above the cut-off of the scales, but this information was not available. Finally, we could not distinguish apathy from PD progression or other neuropsychiatric symptoms. Meta-regression found several impacting variables but there was little consistency. For example, only one specific UPDRS score was related to an increase in apathy, but the other UPDRS scores in on- and off-medication, pre- and post-operatively, showed no relationship with apathy scores.

## Conclusion

The main result of this meta-analysis is that apathy increases after STN DBS, compared to the pre-operative state or to control groups managed only with medication. This effect was independent of confounding variables, including the reduction of dopaminergic medication. These findings are of clinical relevance to the increasing population of PD patients that will become reliant on STN DBS in the future, and demand further research on the subject. ●

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## Supporting Data

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