



Suicide and suicide attempts after subthalamic nucleus stimulation in Parkinson's disease: a systematic review and meta-analysis

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Abstract

Background Deep-brain stimulation is a well-established, effective treatment for patients with advanced Parkinson's disease. Recent studies examining rates of suicide attempts and suicides after deep-brain stimulation in the bilateral subthalamic nucleus have reported varying results. Using this systematic review and meta-analysis, we aim to obtain a comprehensive understanding of suicidality in Parkinson's patients after subthalamic nucleus deep brain stimulation.

Methods We systematically examined Medline, PubMed, Web of Science, and Embase databases to identify studies published before November 2019 that measured rates of suicidality in Parkinson's patients who underwent subthalamic nucleus stimulation. A meta-analysis of the data from the included studies was conducted using Stata 12.0.

Results A total of 18 studies met the eligibility criteria of this study. We found that the pooled rate of suicidal ideation was 4% (95% CI 0.00–7.2%, range 2–17%). The pooled rate of suicide attempts was 1% (95% CI 1.0–2.0%), while the pooled rate of suicide was 1% (95% CI 0.0–1.0%).

Conclusions Our findings indicate a relatively high rate of suicidality among Parkinson's patients after subthalamic nucleus deep-brain stimulation. It is important for clinicians to carefully monitor psychiatric disorders, especially suicidal ideation and suicide attempts, in Parkinson's patients before and after subthalamic nucleus deep-brain stimulation.

Keywords Parkinson's disease · Deep brain stimulation · Subthalamic nucleus · Suicide · Psychiatric disorders

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and its treatment continues to be a challenge [1]. Currently, deep-brain stimulation (DBS) is the most well-established and effective treatment for advanced PD patients presenting with motor complications as a result of standard pharmacological treatment. The most common target of DBS in PD patients is the bilateral subthalamic nucleus (STN) due to its alleviation of motor symptoms and dopaminergic treatment [2].

Prospective and retrospective studies addressing various aspects of suicidality after subthalamic nucleus deep-brain stimulation (STN DBS), including suicide attempts and suicides, as well as suicidal depression and suicidal ideation, have reported contrasting results, along with a range of suicidality rates (0 to 17%) [3–20]. In order to gain a comprehensive understanding of suicidality in PD patients after STN DBS treatment, we conducted a meta-analysis based on a systematic review of relevant literature. We calculated pooled rates of suicidal ideation, suicide attempts, and suicides.

Materials and methods

This meta-analysis was performed based on the recommendations outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [21].

Search strategy

We performed a systematic review of literature indexed in electronic databases, including Medline, PubMed, Web of Science, and Embase. The following keywords were used for searches: “suicide” or “suicide ideation” or “suicide attempts” and “subthalamic nucleus stimulation” or “deep brain stimulation.” All eligible studies published before November 2019 were included, and no language restrictions were applied. All references cited in the retrieved articles were analyzed in order to identify potentially relevant studies.

Eligibility criteria

We included all observational studies (cross-sectional, case-control, or cohort) that analyzed and reported rates of completed or attempted suicide in patients with PD after STN DBS. All included studies followed the UK PD Society Brain Bank criteria to arrive at a confirmed PD diagnosis.

We excluded studies that did not focus on STN DBS in PD patients, as well as those that reported insufficient data and whose authors did not respond to our requests for additional

information. Discussions, editorials, reviews, case reports, letters, commentaries, and critiques were also excluded.

Data extraction

Two independent investigators (YJX and BYY) systematically reviewed the literature and extracted relevant data. Disagreements were resolved after discussion with the corresponding author (XLY). The following data were extracted from each included study: surname of the first author, year of publication, study design, country of origin of cohort being studied, sample size, age of participants, and suicidality outcomes (rates of suicidal ideation, suicide attempts, suicide).

Statistical analysis

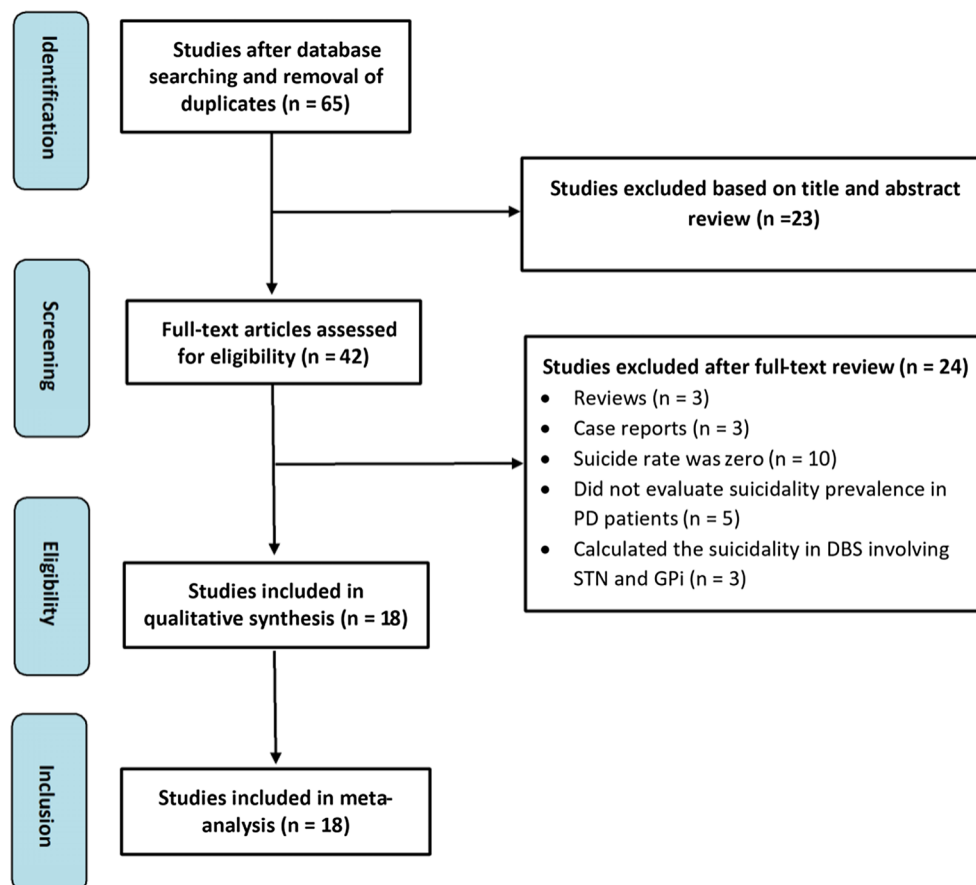
The meta-analysis was conducted using Stata 12.0 (StataCorp, TX, USA). We evaluated data on the rates of suicide ideation, suicide attempts, and suicides among PD patients who underwent STN DBS. The heterogeneity between studies was assessed using the Q test and quantified using the I^2 statistic. I^2 values between 25 and 50% were considered to indicate low heterogeneity, values between 50 and 75% indicated moderate heterogeneity, and values $\geq 75\%$ indicated substantial heterogeneity. All I^2 values below 25% indicated no heterogeneity. When no or low statistical heterogeneity was observed, we used a fixed-effect model for the meta-analysis. In the case of moderate or substantial heterogeneity, a random-effects model was used. Publication bias was assessed using the Egger's and Begg's tests.

Results

Literature screening and assessment

A total of 65 records were identified after examining the databases and removing duplicates (Fig. 1). After eliminating 23 records based on title and abstract, a full-text review was performed for 42 records. A total of 10 studies were automatically excluded by Stata because they reported no cases of suicidal ideation, suicide attempts, or suicides. We also excluded three review articles, three case reports, five studies that did not evaluate the prevalence of suicide in PD patients, and three studies that involved suicidality in patients who underwent DBS in the bilateral globus pallidus interna (GPi).

After a detailed assessment based on eligibility criteria, the final meta-analysis included 18 unique studies involving 6652 PD patients who underwent STN DBS treatment (Table 1). Among these studies, three explored suicidal ideation, 14 investigated rates of suicide attempts, and eight studied rates of suicide in PD patients after STN DBS treatment.

Fig. 1 Flow diagram of study selection

Suicidal ideation among Parkinson's patients after STN DBS

We observed moderate heterogeneity ($I^2 = 54.6\%$) among the three studies addressing suicidal ideation in PD patients after STN DBS. Using the DerSimonian and Laird method, we found that the pooled rate of suicidal ideation was 4% (95% CI 0.00 to 7.2, range 2–17%; Fig. 2). The sensitivity analysis showed that no individual study had a significant effect on the results (Supplementary Fig. 1). No significant publication bias was indicated by Begg's ($p = 0.296$) or Egger's test ($p = 0.101$) (Supplementary Fig. 2).

Suicide attempts among Parkinson's patients after STN DBS

The rates of attempted suicides in PD patients who underwent STN DBS ranged from 1 to 7% across the 14 included studies. Moderate heterogeneity was observed among studies regarding this outcome ($I^2 = 66.6\%$, $p = 0.004$). Using a random-effects approach, we found that the pooled rate of suicide attempts was 1% (95% CI 1–2%; Fig. 3). Although Begg's test indicated a potential publication bias ($p = 0.037$), Egger's test did not ($p = 0.056$) (Supplementary Fig. 3). The sensitivity

analysis showed that no individual study had a significant effect on the results (Supplementary Fig. 4).

Suicides among Parkinson's patients after STN DBS

The rate of suicide among PD patients who underwent STN DBS ranged from 0.6 to 7.1% (Table 1). Sensitivity analysis showed that only one study [21] significantly affected the results (Supplementary Fig. 5); after removing this study from the analysis, the pooled rate of suicide was 1% (95% CI 1–2%; Fig. 4). This result was based on a fixed-effect model since no heterogeneity was observed in the rate of completed suicide across the eight studies ($I^2 = 0$, $p = 0.973$). The funnel plot was visually symmetrical (Supplementary Fig. 6), and Begg's test indicated potential publication bias ($p = 0.035$), but not Egger's test ($p = 0.145$).

Discussion

This meta-analysis examined data from 18 unique studies on suicidality in PD patients who underwent STN DBS. Our results show a high pooled rate of suicidal ideation in these PD patients (4%), while the pooled rates of attempted and completed suicide were both 1%.

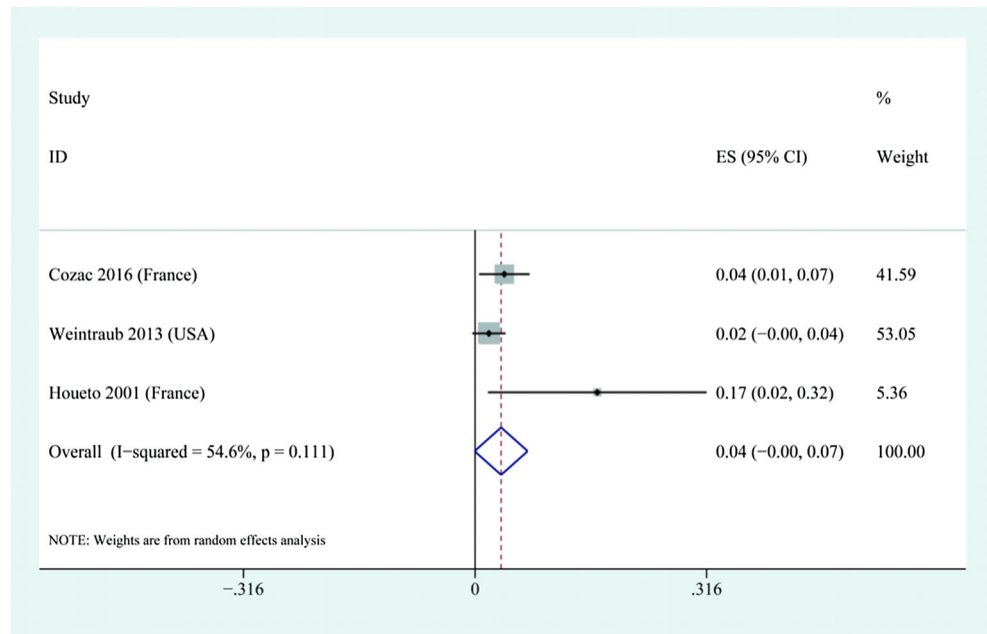
Table 1 Characteristics of studies included in the meta-analysis

Name of author	Year	Design	Country	Suicidality assessment measures	Number of patients	Mean age at DBS (year)	DBS type	Follow-up duration	Suicidality outcomes
Giannini	2019	Case-control	France	Medical records	534	53.6 ± 9.2	Bilateral STN DBS	9.19 ± 5.93 years	Suicide: 4/534(0.75), suicide attempt: 24/534
Lhommée	2018	Open-label randomized	France and Germany	Medical dictionary for regulatory activities	121	52.9 ± 6.6	Bilateral STN DBS	2 years	Suicide: 2/121
Haidar	2017	Prospective, open-label, multicenter	Germany	Medical records	120	62.1 ± 8.3	Bilateral STN DBS	5 months	Suicide attempt: 1/120
Cozac	2016	Observational	France	BDI II	124	52.9 ± 6.6	Bilateral STN DBS	2 years	Suicidal ideation: 1/124, suicide attempt: 2/124, suicide: 2/124
Weintraub	2013	Randomized controlled trial	USA	5-point Likert item	139	NA	STN DBS	6 months	Suicidal ideation: 2 (1.5%), suicide attempt: 1/139
Lhommée	2012	Observational	France	Medical records	63	57.8 ± 7.2	STN DBS	12 ± 1 months	Suicide attempt: 2/63
Strutt	2012	Case-control	USA	BDI	17	63.0 ± 8.86	Bilateral STN DBS	6 months	Suicide attempt: 1/17
Toft	2011	Observational	Norway	Electronic patient record system in hospital	131	60.3 ± 7.8	STN DBS	3.3 years	Suicide: 2/144
Umemura	2011	Observational	Japan	Medical records	180	63.8	Bilateral STN DBS	3–87 months	Suicide attempt: 2/180
Rodrigues	2009	Observational	Portugal	Interview with a psychologist	105	NA	STN DBS	36 months	Suicide attempt: 3/105
Soulas	2008	Observational	France	Interview with a psychologist	158	61.8 ± 8.6	Bilateral STN DBS	12.0 ± 7.2 months	Suicide: 2/158, suicide attempt: 4/158
Tir	2007	Observational	France	Medical records	103	58.7 ± 8.2	Bilateral STN DBS	12 months	Suicide attempt: 1/103, suicide: 1/103
Michael	2007	Observational	France	Medical records	171	59 (range 40–71)	Bilateral STN DBS	41 months	Suicide: 1/171
Funkiewicz	2004	Observational	France	Medical records	77	55 ± 8	STN DBS	3 years	Suicide attempt: 4/77, suicide: 1/77
Voon	2008	Case-control	USA	Suicide risk factor questionnaire	5311	NA	STN DBS	48 months	Suicide: 24/5311, suicide attempt: 48/5311
Krack	2003	Observational	France	Annual interview with the same neuropsychologist	42	55 ± 7.5	Bilateral STN DBS	5 years	Suicide attempt: 3/42
Doshi	2002	Observational	India	Medical records and psychological charts	31	NA	Bilateral STN DBS	NA	Suicide attempt: 1/31
Houeto	2002	Observational	France	Mini international neuropsychiatric inventory	24	NA	Bilateral STN DBS	19 ± 11 months	Suicide risk: 4/24

Includes suicidal ideation and suicide attempts, but not suicides

BDI Beck Depression Inventory, DBS deep brain stimulation, NA not available, PD Parkinson's disease, STN subthalamic nucleus

Fig. 2 Forest plot of suicidal ideation among individuals after STN DBS (4%). The X axis indicates the 95% confidence interval. ES, effect size



Several studies have reported an association of STN DBS with suicidal ideation [5, 22], suicide attempts [3], and suicide [20]. In contrast, certain studies reported no suicides in their cohorts [23, 24], including one that collected follow-up data for 10 years [25]; these studies did not, however, report suicide attempts or suicidal ideation. A multicenter study addressing suicide after STN treatment among 5311 PD patients reported a suicide attempt rate of 0.4% and a suicide rate of 0.2% [12]. In a study comparing PD patients with the general population, the suicide rate among PD patients (0.08%) was

10 times lower than in the general population (0.8%) [26]. Our meta-analysis indicated much higher rates of suicide attempts (1%) and suicide (1%). Further studies of suicide attempts and suicidal ideation are critical to gain a better understanding of the association between STN DBS and suicidality.

An association between DBS and suicidality may be due to the ability of STN DBS to increase the risk of impulse control disorders [27, 28]. DBS may affect STN structure, and striatal lesions can contribute to suicidal behavior and impulsivity [29]. In pallidal and thalamic DBS, disturbance of the basal

Fig. 3 Forest plot of suicide attempt among individuals after STN DBS (1%). The X axis indicates the 95% confidence interval. ES, effect size

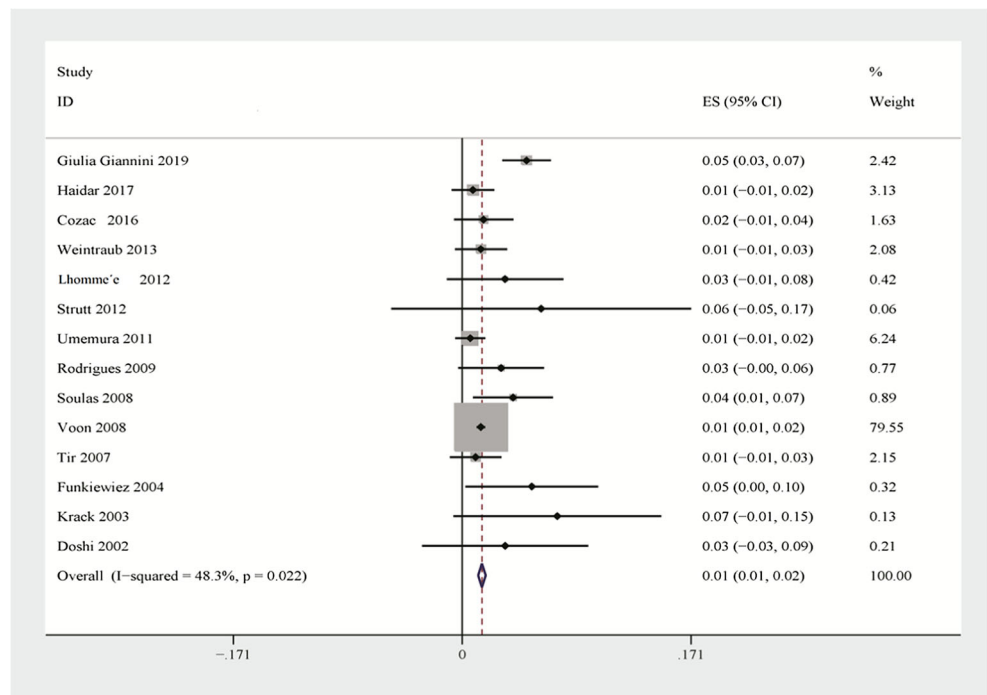
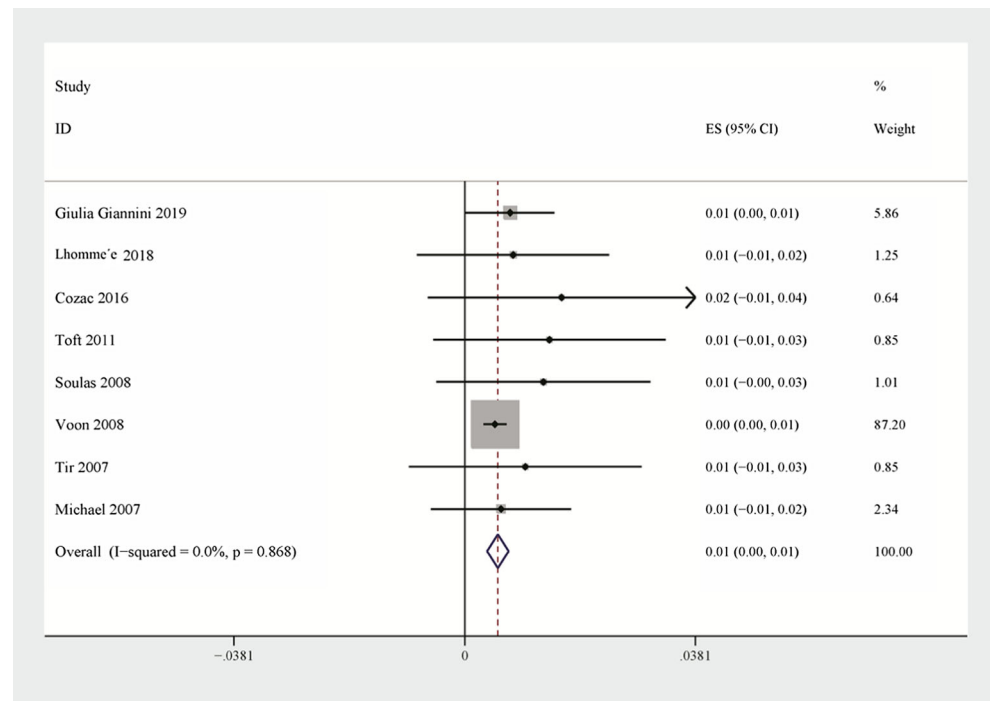


Fig. 4 Forest plot of complete suicide among individuals after STN DBS (1%). The X axis indicates the 95% confidence interval. ES, effect size



ganglia circuitry, especially in the limbic component, may also induce mood disorders and/or suicidal ideas [30]. STN DBS may also interact with existing psychiatric comorbidities, leading to, for example, transient or chronic depression in 25% of PD patients after STN

DBS [31]. Another study showed a 73% decrease in total levodopa equivalent doses immediately after DBS surgery, leading to an increase in apathy (3 vs. 13 patients before and after surgery), with two patients committing suicide [32].

Table 2 Assessment of potential risk factors for suicide in patients with Parkinson's disease

Risk factor	Study	Result
Male sex	Myslobodsky M [26], Lee 2016 [35], Mainio A [36]	Increased risk
European/American ethnicity	Myslobodsky M [26]	Increased risk
Living in rural areas	Mainio A [37]	Increased risk
Education qualification	Myslobodsky M [26]	No effect
Marital status	Myslobodsky M [26]	No effect
Comorbidities	Myslobodsky M [26], Mainio A [36]	Decreased risk
Employment status	Brown GK [37]	Increased risk
Suicidal ideation	Brown GK [37]	Increased risk
Hopelessness	Brown GK [37]	Increased risk
Depressive disorder	Brown GK [37], Yoshimasu K [38], Lee [35]	Increased risk
Bipolar disorder	Brown GK [37], Yoshimasu K [38]	Increased risk
Alcohol/substance-use disorder	Yoshimasu K [38]	Increased risk
Psychosis	Lee [35]	Increased risk
Higher L-Dopa dosage	Lee [35]	Increased risk
Initial extremity of motor Symptom onset	Lee [35]	Increased risk
History of self-harm or past suicide attempts	Mainio A [36]	Increased risk
DBS STN	Voon [12]/Weintraub [13]	Increased risk/no effect
DBS Gpi	Weintraub [13]	No effect

DBS deep-brain stimulation, Gpi globus pallidus internus, L-Dopa L-levodopa, STN subthalamic nucleus

The GPi is another target of DBS treatment in PD patients. A meta-analysis of randomized controlled trials indicated that stimulation of the STN or GPi is equally effective at improving motor symptoms and dyskinesia in PD patients [33]. Whether GPi stimulation exerts similar effects as STN stimulation on cognitive and psychiatric symptoms remains unclear [34]. GPi DBS may be less likely than STN DBS to lead to depression or suicidal ideation/behaviors because patients are more likely to continue their dopaminergic therapy after stimulation of the GPi than after stimulation of the STN [13]. Future studies should explore the effects of different types of DBS along with postoperative drug therapy on suicidality among PD patients.

To understand factors that may contribute to risk of suicide among PD patients, we evaluated reports of risk factors contributing to suicidality. We found that mood (e.g., hopelessness, depression, bipolar disorder), alcohol/substance-use disorders, and a history of self-harm or suicide attempts were associated with higher risk of suicide (Table 2) [26, 35–38]. PD patients who attempt or commit suicide appear to show more frequent suicidal ideation or suicide attempts, more severe psychotic symptoms, higher Beck Depression Inventory scores, and greater use of psychotropic medication than patients who do not attempt or complete suicide [4]. Patients who commit suicide may also show higher levels of sadness, discouragement, failure, guilt, self-disappointment, self-criticism, and lack of interest than those who do not [10]. Future work should clarify the effects of these various risk factors on frequency of suicidal ideation or behaviors and on how often these behaviors end in suicide.

Our results must be interpreted with caution since most of our data were collected from observational studies with varied sample sizes and follow-up durations, leading to underestimation of suicidality. Another limitation that must be addressed in future work is the automatic exclusion of studies with a suicidality rate of zero. The publication bias observed in our study could be due to the fact that some large studies focused on the improvement of motor symptoms rather than suicide rates. Therefore, our results should be verified in large studies involving long follow-up.

In conclusion, the results of our meta-analysis indicate a relatively high suicide rate among PD patients after STN DBS. However, since there are a number of risk factors contributing to suicidality, our finding should not serve as a general contraindication against STN DBS as an effective treatment for PD. Instead, it emphasizes to clinicians the importance of careful monitoring of psychiatric disorders, especially suicidal ideation and suicide attempts, in PD patients before and after DBS [39]. Future studies using animal models should further explore the association between DBS and suicidality, as well as identify optimal regions in the brain that can be used as a target for DBS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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