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Review

A Systematic Review of the Biological Processes Involved in Deep-Brain Stimulation for Parkinson's disease: A Focus on the Potential Disease-Modifying Effects

Francesco Sciancalepore [1, 2, *], Giulia Remoli [2], Leonardo Tariciotti [3, 4], Giulia Sarti [1], Federica Trentin [5], Gabriele Riccardi [6], Eleonora Lacorte [2], Massimo Corbo [7], Marco Canevelli [1, 2], Nicola Vanacore [2], Paola Piscopo [8]

1. Department of Human Neuroscience, "Sapienza" University of Rome, Rome, Italy; E-Mails: sciancalepore.francesco19@gmail.com; giusarti95@gmail.com; marco.canevelli@iss.it
2. National Center for Disease Prevention and Health Promotion, Italian National Institute of Health, Viale Regina Elena, 299, 00161 Rome, Italy; E-Mails: giulia.remoli@guest.iss.it; eleonora.lacorte@iss.it; nicola.vanacore@iss.it
3. Unit of Neurosurgery, IRCSS Fondazione Cà Grande Ospedale Maggiore Policlinico, University of Milan, Via Francesco Sforza, 35, 20122 Milan, Italy; E-Mail: leonardotariciottimd@gmail.com
4. Department of Oncology and Hemato-oncology, University of Milan, Via Festa del Perdono 7, 20122 Milan, Italy
5. Department of Oncological and Degenerative Spine Surgery, IRCCS, Rizzoli Orthopedic Institute, Via G.C. Pupilli, 1, 40136 Bologna, Italy; E-Mail: federicatrentin94@gmail.com
6. Department of Sense Organ, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome, Italy; E-Mail: ric.gabriele@gmail.com
7. Department of Neurorehabilitation Sciences, Casa Cura Policlinico, Via Dezza 48, 20144 Milan, Italy; E-Mail: m.corbo@ccppdezza.it
8. Department of Neuroscience, Italian National Institute of Health, Viale Regina Elena, 299, 00161 Rome, Italy; E-Mail: paola.piscopo@iss.it

* **Correspondence:** Francesco Sciancalepore; E-Mail: sciancalepore.francesco19@gmail.com

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Abstract

Deep-Brain Stimulation (DBS) is an important treatment option for the management of Parkinson's disease (PD) and is a common symptomatic treatment. However, an increasing number of studies have examined the biological processes to assess if DBS can also modify the natural history of PD by acting on its pathophysiological mechanisms. Relevant literature published up to November 2020 was systematically searched on databases such as PubMed, ISI Web of Knowledge, Academic Search Index, and Science Citation Index. The following predefined inclusion criteria were applied to the full-text versions of the selected articles: i) recruiting and monitoring of PD subjects that were previously treated with DBS and ii) investigating the electrophysiological, biochemical, epigenetic, or neuroimaging effects of DBS. Studies focusing exclusively on motor and clinical changes were excluded. Reviews, case reports, studies on animal models, and computational studies were also not considered. Out of 2,960 records screened, 43 studies met the inclusion criteria. Only three studies described a potential disease-modifying effect of DBS. However, a wide heterogeneity was observed in the investigated biomarkers, and the design and methodological issues of several studies limited their ability to find potential disease-modifying features. Specifically, 60.4% of the trials followed-up subjects for no more than 1 year from the surgical intervention, and 67.4% observed patients with PD only once after DBS. Moreover, 64.2% of the studies enrolled late-stage PD patients. Most of the studies (88.4%) reported that DBS only had a symptomatic effect, with several of them showing some limitations in the study design and recruitment of patients. Further studies using shared biomarkers are encouraged to assess if and how DBS might affect the progression of PD. Based on the existing preclinical literature, prospective clinical trials examining the course of PD in early-stage patients are needed.

Keywords

Deep brain stimulation (DBS); Parkinson's disease (PD); disease-modifying; systematic review; biomarkers

1. Introduction

Parkinson's disease (PD) is the second-most common neurodegenerative disorder with a prevalence of 2–3% in individuals aged ≥ 65 years [1]. PD is characterized by motor signs such as bradykinesia, resting tremor, muscular rigidity, and postural disturbances. Its clinical manifestations also include a broad spectrum of non-motor symptoms, including cognitive changes, mood disorders, and autonomic dysfunctions. The main underlying neuropathological hallmarks of PD are the intracellular accumulation of misfolded α-synuclein, and the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [1, 2].

There are currently no available disease-modifying treatments for PD. The main intervention to manage motor symptoms is dopamine replacement through L-Dopa. Dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and non-dopaminergic drugs (i.e., anticholinergics and amantadine) are also used as symptomatic agents [3].

Another treatment option is Deep Brain Stimulation (DBS), which is considered to be a useful strategy to manage motor symptoms. DBS is a surgical procedure that involves the delivery of continuous electrical stimulation to a given neural target through chronically implanted electrodes [4]. DBS has been associated with some relevant side effects such as behavioral changes, depression, and cognitive impairment [5–8]. However, most studies have found it to be safe and well-tolerated [9]. Electrodes are often inserted in the Subthalamic Nucleus (STN) or the internal Globus Pallidus (GPi), as several clinical trials have established that the stimulation of these two areas is often associated with an improvement of motor symptoms in patients with PD [9, 10].

To date, the exact mechanisms underlying the effects of this neurosurgical procedure have only been partially elucidated. The main current theory on the underlying mechanism of DBS is that it induces changes in the firing pattern of the basal ganglia structures and pathways by inhibiting or exciting neuronal activity in the STN or GPi. For example, the neuronal activity in the GPi was observed to increase after DBS in the STN [11]. Another theory called “the disruption hypothesis” has proposed that DBS dissociates both input and output information and blocks unusual signals through the cortico-basal-ganglia loop [12]. Overall, these hypotheses suggest that the effects induced by DBS are only transient, supporting the common opinion within the neurological community that DBS, like pharmacological therapies, is not a disease-modifying treatment for PD [12, 13]. Accordingly, some studies have reported DBS to be a symptomatic treatment with limited long-term improvements [14, 15]. However, increasing studies have focused on investigating the biological and neurophysiological correlations of DBS to find a potential disease-modifying effect on the progression of PD. Accordingly, some preclinical studies have suggested the association of STN-DBS with an improvement of dopaminergic neuron survival and an increase in the levels of Brain-Derived Neurotrophic Factor (BDNF), suggesting a long-term neuroprotective effect [16, 17]. This hypothesis could also be associated with the functional inhibition of STN by DBS, which reduces the toxicity of nigral glutamate. However, it is not supported in humans, probably due to the use of DBS in patients with late-stage PD [18, 19].

Therefore, this study aimed to systematically review and discuss the existing evidence on the biological effects associated with DBS treatment in patients with PD to explore the potential disease-modifying features of this treatment. The objective of this study was to understand if DBS could be considered only as a symptomatic treatment for PD or if it may induce modifications that might affect the natural history of PD by acting on its pathophysiological mechanisms.

2. Methods

This systematic literature review was performed according to the methodology described in the Cochrane handbook for systematic reviews [20] and was reported based on the PRISMA statement for reporting systematic reviews and meta-analyses [21]. All the literature published up to November 2020 was retrieved by a thorough search of the databases “PubMed”, “ISI Web of Knowledge”, and “Discovery” using the search terms parkinson* AND ("deep brain stimulation"

OR "deep brain stimulations" OR "DBS") AND (biol* OR chemi* OR biochemi* OR bio-chemi* OR neurobiol* OR neuro-biol* OR neurochem* OR neuro-chemi* OR biomark* OR neurophysiol* OR neuro-physiol* OR "disease modifying" OR "disease modify" OR disease-modifying OR disease-modify OR "disease modification" OR neuroprotect*).

No limitations in the search strategy were applied to the date of publication, study design, or language. References of the selected studies were also searched to identify any further relevant data.

The title and abstracts of the identified records were initially screened and selected by six independent reviewers (FS, GR, PP, GS, FT, and GR) based on their pertinence to the review topic. Disagreements were resolved by a consensus.

The following set of predefined inclusion criteria were then individually applied to the selected articles in their full-text version: i) recruiting and monitoring of PD subjects that were previously treated with DBS and ii) investigating the electrophysiological, biochemical, epigenetic, or neuroimaging effects of DBS. Studies with an exclusive focus on motor and clinical changes were excluded. Reviews, case reports, studies on animal models, and computational studies were also not considered. Articles not published in English were removed. Systematic reviews were considered separately to check the consistency of data.

Data were extracted by three pairs of independent reviewers (GR and LT, PP and GS, FT and GR) using specifically designed tables. The main clinical and demographic features of all included studies were first reported in an introductory table (Table 1), while the analytical procedures and results from the biochemical and epigenetic studies (Table 2a) and neurophysiological studies (Table 2b) were reported in another table.

Table 1 Clinical and demographic data of the included studies according to the type.

Study	Diagnostic criteria	Surgery selection criteria	DBS	Pharmacological interventions	Follow-up (When)	Participants (number; mean age; female/male) Cases	Controls	UPDRS pre and post-surgery (cases)
BIOCHEMICAL								
Constantinescu 2011 [22]	PD (UK Parkinson's Disease Brain Bank criteria)	NR	STN Bilat.	NR	1 pre-DBS 4 post-DBS (1 week; 2 weeks; 4.5 months; 1 year)	8; 58.5 (51–63); 2/6	-	NR
Constantinescu 2018 [23]	PD (Not specified criteria)	NR	STN Bilat	L-DOPA, apomorphine, COMT-inhibitors, MAO-B inhibitors, and amantadine	>1 pre-DBS (during 1 year) ≥2 post-DBS (during 11 years)	16; 64 (55–75); 6/10	-	NR
Dong 2019 [24]	PD (Movement Disorder Society criteria)	NR	NR	NR	1 post-DBS (1 month)	4 PD1 (NO DBS) 4 PD2 (DBS OFF) 4 PD3 (DBS ON); 72 (65–79); 4/8	12; 69 (65–71); 3/9	NR

Guimaraes 2013 [25]	PD (NR)	No surgical contraindications	STN Bilat.	Levodopa 1004 ±102 mg/day	1 pre-DBS (1 week) 2 post-DBS (1 week; 2 months)	23; 64 ±7; 5/18	-	Pre: 45 ±12 Post: 14 ±7 (1 week); 13.8 ±7.2 (2 months)
Kwiatek-Majkusiak 2018 [26]	PD (UK Parkinson's Disease Brain Bank criteria)	NR	STN Bilat.	L-DOPA and dopamine agonist (ropinirole)	1 post-DBS (mean: 28.4 months)	37 MT-PD 15 DBS-PD; MT-PD: 57.2 ±11.5 DBS-PD: 54.4 ±8.4; MT-PD: 18/19 DBS-PD: 7/8	31; 58.1 ±2.5; 15/16	Pre: NR Post: MT-PD: 33.5 ±16 DBS-PD: 40.1 ±11.8 (DBS OFF) MT-PD: 12.2 ±7.6 DBS-PD: 9.2 ±4.8 (DBS ON)
Kwiatek-Majkusiak 2020 [27]	PD (UK Parkinson's Disease Brain Bank criteria)	NR	STN Bilat.	L-DOPA and dopamine agonist (ropinirole)	1 post-DBS (mean: 30.28 months)	47 MT-PD 13 DBS-PD; MT-PD: 60.17 ± 10.36 DBS-PD: 53.62 ± 10.94; MT-PD: 21/26 DBS-PD:	28; 58.44 ±2.35; 14/14	Pre: NR Post: MT-PD: 35.78 ±13.15; DBS-PD: 50.92 ±13.3 (DBS OFF) MT-PD: 12.85 ±10.99; DBS-PD: 10.69 ±5.28

						6/7		(DBS ON)
Mallach 2019 [28]	PD (UK brain bank Criteria)	Improvement in cardinal motor symptoms of PD	STN	NR	1 post-mortem (≥5 years of DBS)	3 DBS-PD 4 PD; DBS-PD: 76.3 ±4.0 PD: 70.0 ±3.3; NR	3; 67.0 ±3.1; NR	-
Pal 2017 [29]	PD (NR)	NR	STN Bilat.	NR	1 post-mortem (mean: 52.1 months)	11 DBS-PD; 57.6 ±7.7; NR	156 MT-PD; 67.4 ±10.6; NR	NR
Pienaar 2014 [30]	PD (Neuropathological diagnosis)	NR	STN	NR	1 post-mortem	5 DBS-PD 7 MT-PD; DBS-PD: 80±1.17 MT-PD: 76±6.84; DBS-PD: 2/3 MT-PD: 3/4	7; 77±12.13; 3/4	NR
Seifried 2013 [31]	PD (UK Brain Bank criteria)	NR	STN Bilat.	Levodopa equivalence dose (LEDD) 1050 ±300 mg	1 pre-DBS 2 post-DBS (3 months; 6 months)	11; 63 ±7; 6/5	-	Pre: 49.09 ±21.04 Post: 28 ±15 (3 months) (DBS ON)

Vedam-Mai 2014 [32]	PD (Neuropathological examination)	NR	7 bilateral STN 1 left STN 2 GPi bilat. 1 GPi left 1 VIM bilat.	NR	1 post-mortem (mean: 4.2 years of DBS)	12 DBS-PD 5 PD; DBS-PD: 71.7 PD: 79.3; DBS-PD: 3/9 PD: 0/5	10; 75.4; 4/6;	-
Wang 2013 [33]	PD (not specified criteria)	Benabid and Lang criteria	STN Bilat.	Levodopa 1500–2000 mg per day	1 pre-DBS (1 day) 4 post-DBS (1 week; 3 months; 1 year; 2 year)	6; 62.83 ±2.4; 3/3	6; 62.83 ±2.4; 3/3	Pre: 67.67 ±8.69 Post: 31.67 ±5.54 (1 week); 27.1 ±3.92 (3 months) 33.33 ±20.68 (1 year); 33.33 ±21.02 (2 years) (DBS ON)
EPIGENETIC								
Soreq 2012 [34]	PD (fulfilled detailed medical history questionnaires)	NR	STN Bilat.	7 DRT 2 patients: anti-hypertension medication 1 hyperlipidemia treatment	1 pre-DBS 2 post-DBS (mean: 2.2 months; 1 h of OFF DBS)	7; 55.85 ±4.14; 0/7	6; NR; 0/6	NR

Soreq 2013a [35]	See above	See above	See above	See above	See above	See above	See above	See above
Soreq 2013b [36]	See above	See above	See above	See above	See above	See above	See above	See above
Soreq 2014 [37]	See above	See above	STN Bilat.	NR	See above	3; 52.7; 0/3	3; 60.7; 0/3	Pre: NR Post: 34 (DBS ON) 42.5 (DBS OFF)
ELECTROPHYSIOLOGICAL								
Airaksinen 2012 [38]	PD (NR)	NR	STN Bilat.	Optimized antiparkinsonian medical therapy	1 post-DBS (mean: 1.02 years)	11; 61.4 ±6.7; 6/5	-	Pre: NR Post: 27.7 ±12.9
Anidi 2018 [39]	Patients with history or presenting freezing of gait (FOG) during tasks were defined "Freezers". Patients not presenting FOG were defined "Non-Freezers"	NR	STN Bilat.	Long-acting dopaminergic medications	1 post-DBS (≥21 months)	9 Freezers; 62.21 ±7.10; 4/5	4 Non Freezers; 62.37 ±8.12; NR	Pre: 45.17 ±7.83 (Meds OFF) 19.57 ±8.66 (Meds ON) Post: 36.38 ±10.20 (DBS OFF) 12.63 ±7.21 (DBS ON)
Dauper 2002 [40]	Akinetic-rigid PD (NR)	NR	STN Bilat.	Optimized antiparkinsonian medical therapy	1 post-DBS (≥3 months)	8; 59.3 ±10.0; 4/4	10; NR; 6/4	Pre: 10.8 ±7.1 (1 PD patient) Post:

								46.6 ±12.7 (DBS OFF) 24.1 ±11.5 (DBS ON)
Fraix 2008 [41]	PD (Hoehn and Yahn criteria)	Off medications	STN Bilat.	Off-medication condition for at least 12 h	2 post-DBS (3 months; 9 months)	15; 60.0 ±11.0; 3/12	-	Pre: 44.4 ±14 Post: 15.2 ±8.0 (DBS ON)
Giannicola 2012 [42]	NR	NR	STN Bilat.	Antiparkinsonian medication	1 During DBS (intraoperative group); 1 post-DBS (mean: 7.54 years, hyperchronic group)	Acute group: 16; 59.6 ±9.1; 6/10	Hyperchronic group: 11; 61.0 ±12.2 5/6	NR
Gulberti 2015 [43]	PD (Hoehn and Yahr criteria)	Hoehn & Yahr criteria	STN Bilat.	Preoperative: DOPA ON/DOPA OFF Postop: DOPA OFF	1 post-DBS (mean: 5 months)	12; 61.0 ±6.0; 7/5	12; 65.0 ±8.0; 7/5	Pre: DOPA OFF: 32.0 ±12.0 DOPA ON: 18.0 ±9.0 Post: 20 ±0.8 (DBS ON)
Jech 2006 [44]	PD (NR)	NR	STN Bilat.	Off-medication condition for at least	1 post-DBS (mean: 9.9 months)	12; 57.3 ±6.3; 5/7	-	Pre: 44.8 ±14.4 Post: 23.3

				12 h				±12.0 (DBS ON) Pre: 51.1 ±19.0 Post: 26.7 ±7 .7 (DBS ON) Pre: 73.9 ±10.2 Post:
Michmizos 2015 [45]	PD (Hoehn and Yahn criteria)	CAPSIT criteria	STN Bilat.	NR	1 post-DBS (≥2 years)	9; NR; NR	11; NR; NR	
Pierantozzi 1999 [46]	PD (Hoehn and Yahr criteria)	Hoehn and Yahr criteria	4 bilateral GPi-DBS 2 bilateral STN-DBS	Dopaminergic therapy before and after 3 h of apomorphine infusion.	1 post-DBS (mean: 6 months)	6; 51.6; NR	-	GPi-DBS: 17.0 ±7.7 (DBS ON); STN-DBS: 20.0 ±1.4 (DBS ON) Pre: NR Post:
Ray 2008 [47]	PD (NR)	Localization of the subthalamic nucleus using Radionics Image Fusion and Stereoplan combined with field potential recording	STN Bilat. (except one patient, which was implanted monolaterally)	Off assessment: overnight withdrawn. On assessment: 1,5 h after administration Type of medication: NR	1 post-DBS (3 months)	7; 59.6 ±2.8; NR	-	The off drugs motor UPDRS scores ↓ 41% (p = 0,01); the bradykinesia/rig idity UPDRS scores ↓ 37% (p = 0,01) the tremor UPDRS scores

								↓ 59% (p = 0.05)
Rosa 2011 [48]	PD (NR)	LIMPE: Guidelines for the treatment of Parkinson's Disease	STN Bilat.	Antiparkinsonian medication (Levodopa)	1 post-DBS (1 months)	7; 66.8 ±5.4; 1/6	-	Pre: DOPA ON: 19.7 ±5.0 DOPA OFF: 37.7 ±4.3 Post: NR
Sinclair 2018 [49]	PD (NR)	NR	STN Bilat.	Levodopa	1 post-DBS (≥3 months)	14; 60.6 ±6.6; 5/9	-	NR
Trager 2016 [50]	Akinetic rigid (AR) or Tremor dominant (TD), using the following criteria (Quinn et al., 2015)	Clinical motor outcome of bilateral subthalamic nucleus deep-brain stimulation for Parkinson's disease using image-guided frameless stereotaxy (Bronte-Stewart et al. 2010)	STN Bilat.	Long-acting dopaminergic medications were withdrawn over 24 h and short-acting medication was withdrawn over 12 h before surgery	1 pre-DBS 1 post-DBS OFF (1 month) 2 post-DBS ON (6 months; 1 year)	17; 61.6 ±8.04; 5/12	-	Pre: 42.5 ±10.6 Post: ↓ score p = 0.04 (12 months)
Weiss 2015	PD (NR)	Hoehn and Yahr criteria	STN Bilat.	Levodopa	1 post-DBS (mean: 2.9	20; 58.6 ±9.4;	-	Pre: 57.0 ±13.6

[51]					years)	5/15		Post: 22.3 ±9.7 (DBS ON)
NEUROIMAGING								
Dong 2020 [52]	"Definite diagnosis of idiopathic PD" (NR criteria)	NR	STN Bilat.	Compound levodopa and dopamine receptor agonists	1 pre-DBS 1 post-DBS (3 months)	23; 60.91 ±12.62; 14/9	14; 63.29 ±9.72; 7/7	Pre: 39.30 ±12.47 Post: NR
Ge 2020 [53]	PD (UK Parkinson's Disease Brain Bank criteria)	NR	PD2: STN Bilat.	Oral antiparkinsonian treatment	1 pre-DBS 2 post-DBS (3 months: 1 year)	PD1:33 PD2: 9; PD1: 58.1 ±10.3 PD2: 63.1 ±9.2; PD1:18/15 PD2:5/4	HC1: 33 HC2: 9; HC1: 57.4 ±10.5 HC2: 61.7 ±7.3; HC1: 18/15 HC2: 5/4	Pre: PD1: 25.2 ±14.4 PD2: 49.7 ±8.4 Post: PD2: 27.4 ±17.3 (3 months; DBS OFF) PD2: 49.3 ±18.2 (1 year; DBS OFF)
Hanssen 2019 [54]	PD (Movement Disorder Society criteria)	NR	STN Bilat.	Levodopa equivalence dose of 552 ±351 mg/day	1 post-DBS (mean: 2.2 years)	26; NR; NR	-	Pre: NR Post: ↑ 26.4 ±15.5% of the UPDRS-III

								(DBS OFF)
Hilker 2004 [55]	PD (UK Parkinson's disease Brain Bank criteria)	Not specified criteria	STN Bilat.	Levodopa	1 pre-DBS (3 weeks) 1 post-DBS (mean: 3.8 months)	8; 61.8 ±7.7; 3/5	10; 62.6 ±3.6; 4/6	Pre: 43.5 ±15.5 Post: 45.6 ±12.1(DBS OFF)
Hilker 2005 [56]	PD (UK Parkinson's disease Brain Bank criteria)	CAPSIT criteria	STN Bilat.	Levodopa equivalence dose 150–300 mg/day	1 pre-DBS (mean: 1 months) 1 post-DBS (mean: 16 months)	30; 59.8 ±7.2; 11/19	-	Pre: 42.9 ±11.4 Post: 20.4 ±8.4 (DBS ON)
Lokkegaard 2007 [57]	PD (CAPSIT criteria)	CAPSIT criteria	STN Bilat.	Levodopa 832 ±396 mg/day	1 pre-DBS 2 post-DBS (3 months; 1 year)	35 DBS-PD; 59 ±8.1; NR	10 MT-PD; 64 ±6.8; NR	Pre: 51 ±14 Post: ↑ of the score p = 0.002 (1 year; DBS OFF)
Mubeen 2018 [58]	PD (NR)	NR	STN Bilat.	Levodopa 450 mg	1 post-DBS (mean: 2.2 years)	7; 57; 0/7	-	Pre: NR Post: 35.6 (DBS OFF)
O'Gorman Tuura 2018 [59]	PD (NR)	NR	STN Bilat.	Levodopa (9 Patients) Levodopa + dopamine agonists (7 patients)	1 pre-DBS 1 post-DBS (6 months)	16 (14 DBS); 65; 3/13	16; 62; 4/12	Pre: 61.6 Post: 36.9 (DBS ON)

Palard-Novello 2020 [60]	PD (UK Parkinson's disease Brain Bank criteria)	Australian guidelines (Movement Disorder Society of Australia)	GPi Bilat.	Levodopa equivalent daily dose 1446 ±6 27 mg	1 pre-DBS (4 months) 1 post-DBS (4 months)	32; 60.9 ±7.7; 17/15	-	Pre: 39 ±15 Post: 26 ±13 (DBS ON)
Peron 2010 [61]	PD (UK Parkinson's disease Brain Bank criteria)	Not specified	STN Bilat.	Levodopa equivalent daily dose 1081.1 ±605.3 mg	1 pre-DBS (3 months) 1 post-DBS (3 months)	13; 53.3 ±8.5; 5/8	13; NR; 5/8	Pre: 31.4 ±12.2; Post: 14.1 ±7.4 (DBS ON)
Sidtis 2012 [62]	PD (NR)	NR	STN Bilat.	Levodopa 450 mg	1 post-DBS (mean: 2.2 years)	7; 57.1; 0/7	-	Pre: NR Post: 35.6 (DBS OFF)
Smith 2019 [63]	PD (UK Parkinson's disease Brain Bank criteria)	CAPSIT and NICE criteria	STN Bilat.	Levodopa	1 pre-DBS 1 post-DBS (mean: 5 months)	7; 66 ±7; 3/4	-	Pre: 57.3 ±15.3 Post: 37.6 ± 20 (DBS ON) 54.6 (DBS OFF only 3 patients)
Vassal 2019 [64]	PD (NR)	Not specified	STN Bilat.	Levodopa equivalent daily dose 1497 ±364.5 mg	1 pre-DBS 2 post-DBS (3 months; 6 months)	9; 58 ±6.3; 4/5	-	Pre: 33.8 ±10.6 Post: 17 ±5.5 (DBS ON)

NR (Not reported); - (Absent); DBS-PD (patients with PD treated with DBS); MT-PD (patients with PD treated only pharmacologically); HC (Healthy controls); UPDRS (Unified Parkinson's Disease Rating Scale); STN (Subthalamic nucleus); GPi (Globus Pallidus internus); VIM (Ventral Intermediate nucleus of the thalamus); Bilat. (Bilaterally); FOG (Freezing of Gait)

Table 2a Summary of the analytical procedures and results of the biochemical and epigenetic studies.

Study	**Specimen**	**Sample Processing**	**Analytical procedure of the sample**	**Biomarker**	**Level of biomarker after DBS VS Controls**			
					1st follow-up	**2nd follow-up**	**3rd follow-up**	**4th follow-up**
BIOCHEMICAL								
Constantinescu 2011 [22]	CSF	Storage	ELISA	**NFL**	↑ NFL Levels	↑NFL levels	↓NFL levels	↓NFL levels
Constantinescu 2018 [23]	CSF	Storage	ELISA	**NFL, T-Tau, p-Tau, GFAP, Aβ42**	↑ NFL, t-Tau. GFAP levels	↑NFL, t-Tau, GFAP levels	↓NFL t-TAU, GFAP levels	↓NFL t-Tau, GFAP levels
Dong 2019 [24]	Plasma	Centrifuge	Tandem mass tag markers and liquid chromatography-mass spectrometr-based	**CCDC154, TRIM3, DHH, NRP2, CLIC1**	↓ expression of CCDC154, TRIM3, NHH ↑ expression of NRP2, CLIC1	-	-	-

			techniques					
Guimaraes 2013 [25]	24-h urine	Costar Spin-X microfilter tubes	High-performance liquid chromatography with electrochemical detection	**L-DOPA; DA; Noradrenaline; DOPAC; HVA; 3-MT; DA/L-DOPA; DOPAC/DA; HVA/DA; 3-MT/DA**	↓ L-DOPA P<0.001 ↓DA P<0.005 ↑Noradrenaline P<0.05 ↓DOPAC P<0.05 ↑ DA/L-DOPA P<0.05	↓L-DOPA P<0.001 ↑Noradrenaline P<0.05 ↑ DA/L-DOPA P<0.001 ↓3-MT/DA P<0.005	-	-
Kwiatek-Majkusiak 2018 [26]	Blood	Frozen storage at −80 °C	ELISA	**Pro-hepcidin**	DBS-PD, ↑Pro-hepcidin P<0.001	-	-	-
Kwiatek-Majkusiak 2020 [27]	Blood	Frozen storage at −80 °C	ELISA	**Hepcidin**; **IL-6**	DBS-PD ↑Hepcidin P<0.001 ↑IL-6 P = 0.004	-	-	-
Mallach 2019 [28]	Post-mortem brain	Immunohistofluorescence	-	**Mitochondrial volume of DA synapses in the striatum**	**Distance between mitochondria and presynaptic terminals was**	-	-	-

					↓ in the HC sections in comparison to the PD groups (P<0.05). Mitochondrial volume was ↑ in DBS-PD and similar to the HC (P<0.05)			
Pal 2017 [29]	Post-mortem brain	Immunohistofluorescence	-	**Alpha-synuclein**	The SN pigmented neuron loss score did not differ between the two groups (p = 0.64). DBS subjects had ↑ alpha-synuclein density scores within the SN and locus coeruleus (p = 0.006)	-	-	-
Pienaar 2014	Post-mortem brain	Histopathology, immunofluorescence	-	**VEGF, microvascular**	**In STN-DBS PD samples ↑**	-	-	-

[30]				**changes**	**expression of VEGF and microvessel endothelial cell thickness and length (p<0.001)**			
Seifried 2013 [31]	Blood	Quick freezing and kept at –20 ° C	Hormonal dosage	**Cortisol; ACTH**	1) 15.4 ±6.7 (basal cortisol) 2) 36.2 ±47 (basal ACTH)	1)14.9 ±7.6 µg/dL 2) 23.5 ±19.0 pg/mL	1) 14.0 ±6.1 µg/dL P = 0.89 2) 20.3 ±15.7 pg/mL P = 0.44	-
Vedam-Mai 2014 [32]	Brain slices, post-mortem	Immunohistochemical analysis	-	**PCNA**	**DBS ↑ proliferating cells expressing markers of the cell cycle, plasticity, and neural precursor cells in PD-DBS tissue compared with both normal brain tissue and tissue**	-	-	-

					from patients with PD not treated with DBS (P<0.05). The level of cell proliferation in the SVZ in PD-DBS brains was 2–6 fold greater than that in normal and untreated PD brains			
Wang 2013 [33]	CSF	Centrifuge	2-D DIGE in combination with MALDI-TOF and TOF-TOF mass spectrometry; Western Blotting	21 different proteins such as: **apoA-1, C4, IgA, EC-SOD, IgK protein, myosin, tetranectin**	↑EC-SOD P<0.05 ↑Tetranectin P<0.05	↑EC-SOD P<0.05 ↑Tetranectin P<0.05	↑EC-SOD P<0.05 ↑Tetranectin P<0.05	-
EPIGENETIC								
Soreq 2012 [34]	Blood (leucocytes)		Affymetrix exon array	**Transcript isoforms**	173 Transcripts of patients with PD differ from controls	Pre-DBS vs post-DBS 465 genes differentially	The OFF DBS state was accompanied by	-

					expressed after DBS surgery; post-DBS vs HC 321 transcripts changed between PD patients' post-DBS to HC, including PARK7 and PARK1 which maintained PD-characteristic changes.	differential expression of 351 transcripts	
Soreq 2013a [35]	Blood (leucocytes)	Exon arrays analysis	**MiRNAs**	16 miRNAs modified 332 changed isoforms	Pre-DBS vs post-DBS 11 miRNAs modified 155 changed isoforms	-	-
Soreq 2013b [36]	Blood (leucocytes)	In-house exon array leukocyte dataset	**Alternative Splicing (AS)**	319 AS changed 146 AS changed	Pre-DBS vs post-DBS 254 AS changes	-	-
Soreq 2014 [37]	Blood (leucocytes)	RNA-Seq	**long non-coding RNAs (lncRNA)**	PD vs HC ↓13 lncRNA expression	DBS modified 663 lncRNA (18 lncRNA P<0.05)	-	-

	↓14 lncRNA ↑4 lncRNA

↑ (increased); ↓ (decreased); PD (Parkinsonian patients); HC (Healthy controls); CSF (Cerebrospinal fluid); NFL (neurofilament triplet protein); t-Tau (total-TAU); p-Tau (phosphorylated-tau); GFAP (glial fibrillary acidic protein); Aβ-42 (brain amyloidosis); CCDC154 (coiled-coil domain-containing protein 154); TRIM3 (tripartite motif-containing protein 3); DHH (desert hedgehog protein); NRP2 (neuropilin); CLIC1 (chloride intracellular channel protein 1); IL-6 (interleukine-6); PCNA (Proliferating Cell Nuclear Antigen antibody); ApoA-1 (Apolipoprotein-A1); IgA (Immunoglobulin A); IGK (Immunoglobulin Kappa); EC-SOD (extracellular superoxide dismutase); L-DOPA (levodopa); DA (dopamine); DOPAC (3,4-dihydroxyphenylacetic acid); HVA (chemical homovanilic acid); 3-MT (3-methoxytyramine); DA/L-DOPA (ratio dopamine and levodopa); DOPAC/DA (ratio 3,4-dihydropgenylacetic acid and dopamine); MT/DA (ratio 3-methoxytyramine and dopamine); ACTH (adeno corticotropic hormone); VEGF (vascular endothelial growth factor); miRNAs (microRNAs)

Table 2b Summary of the analytical procedures and results of the neurophysiological studies.

Study	**Type of neurophysiological procedure**	**DBS condition during procedure (ON/OFF)**	**Cerebral areas/pathways**	**Type of analyzed activity**	**Brain activity after DBS VS Controls**		
					1st follow-up	**2st follow-up**	**3rd follow-up**
ELECTROPHYSIOLOGICAL							
Airaksinen 2012 [38]	Spontaneous MEG activity in the somatomotor (mu) and occipital regions (alpha)	ON/OFF	Somatomotor and occipital regions	**Spontaneous activity of somatomotor regions. Occipital region: frequency band around the peak alpha frequency ±2 Hz**	Alpha peak range varied between 5.68 Hz and 10.87 Hz. Source strength decreased from 7.6 to 7.1 nAm p = 0.05	-	-

Anidi 2018 [39]	MER	DBS-OFF, 60 Hz and 140 Hz blinded DBS administration	Bilateral STNs	**LFPs: beta burst power recording**	Both 60-and 140 Hz ↓ duration of bursts compared to no DBS. ↓ pathological beta burst durations and gait impairment P<0.05	-	-
Dauper 2002 [40]	TMS	Stimulator "off"/medication "off" vs Stimulator "off"/medication "on" vs Stimulator "on"/medication "off" vs Stimulator "on"/medication "on"	Right extensor carpi radialis (ECR); muscle and flexor carpi radialis (FCR) muscle.	**Intracortical inhibition**	Stimulation off/med off: inhibition at 3 ms (0,55 ±0,37 p = 0.011); Stimulation on/med off: inhibition at 3 ms (0,57 ±0,18, p<0,001); Stimulation on/med on: inhibition at 3 ms (0,52 ±0,21, p<0,001)	-	-
Fraix 2008 [41]	TMS	(OFF, ON with chronic therapeutic parameters, ON	Hand motor cortex area contralateral to the clinically most affected side	**Intracortical Inhibition**	Longer SP: ON-STN vs OFF-STN (p<0.001). SP elicited at	-	-

		High with a voltage set 10% under permanent side effects threshold)	to evoke optimal responses in the contralateral FDI.		120%MT intensity was shortened under ON High V STN vs ON-STN ($p<0.001$).		
Giannicola 2012 [42]	MER	ON/OFF	Bilateral STNs	**LFPs: beta burst power recording**	No differences in LF activity or beta activity between acute and hyperchronic patients with PD (acute, 9.97 ±3.24% vs hyperchronic, 6.32 ±5.56%, $p = 0.29$)	-	-
Gulberti 2015 [43]	Registration of EEG-activity modulation in response to rhythmic auditory stimulation (RAS)	DOPA OFF + DBS OFF; DOPA ON + DBS ON	EEG activity from 62 active Ag/AgCl scalp electrodes	**Absolute and relative power for the 5 main frequency bands; slow and fast RAS**	Postoperative overall response modulation level was in the range with HC. Both dopaminergic medication and DBS normalized the time course and peak duration of stimulus-driven	-	-

					beta power fluctuations in the fast RAS condition.		
Jech 2006 [44]	EEG. VEPs	DBS-OFF/Med OFF; DBS-ON/Med OFF; (recording after 25 mins)	Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, O1, O2, Fz, Cz, Pz and Oz relative to the left mastoid.	**VEPs; sampled with a frequency of 1000 Hz/channel in the 0.015–75 Hz interval**	BW-VEP: lowering of the N70/P100 amplitude, in proportion to increasing intensity of DBS ($p<0.01$;)	-	-
Michmizos 2015 [45]	MER	ON	Bilateral STNs	**Correlation to beta-band peaks distance from electrode tips during surgery**	The mean distance between beta-band peaks and the electrode's tip was 3.5 ±0.97 mm and 1.0 ±1.14 mm for "poor" and "good" responders, $p = 0.0025$	-	-
Pierantozzi 1999 [46]	SEPs	Preoperative SEPs (no DBS); 6 months after surgery during ineffective and effective DBS state	SEPs were recorded via Ag/AgCl surface electrodes placed in frontal and parietal areas	**Peak latency of parietal waves N20 ±P25 and frontal wave N30**	↑ N30 amplitude with respect to the value observed during `ineffective' DBS (GPi: 4.6 vs 1.5 mV; STN: 4.5 vs 1.2 mV; $p = 0.02$)	-	-

Ray 2008 [47]	MER	ON/OFF	Bilateral STNs	**LFPs: beta burst power recording**	↓ beta power correlated with changes bradykinesia/rigidity UPDRS p = 0.05. Bradykinesia/rigidity improvements predict improvements in bradykinesia/rigidity after DBS, p = 0.05	-	**-**
Rosa 2011 [48]	MER	ON/OFF	STN	**LFPs: beta burst power recording**	No changes in DBS off condition beta activity between the hyperacute and chronic phases	-	-
Sinclair 2018 [49]	MER	ON/OFF. chronic stimulation was ceased 45 min prior to baseline "off-therapy" assessments.	STN	**ERNA**	↑ Dorsal STN ERNA than all other regions (<0.001)	-	-
Trager 2016	LFPs were recorded	ON/OFF	STN	**resting state LPFs: beta burst**	↓ beta band spectra in both	↓ beta band	↓ in beta power

[50]	from electrode pair 0–2 or 1–3 of the DBS lead			**power recording**	STNs at 0, 15, 30, 45, and 60 min after stimulation was turned off. ↓ beta band power correlated with improvement in motor disability scores (P<0.05)	power at 0 and 60 mins p = 0.036, p = 0.005	compared to baseline p = 0.082
Weiss 2015 [51]	64 channel surface EEG	ON/OFF	Bilateral sensorimotor areas ('C3', 'C4'), supplementary motor area ('FCz') and bilateral dorsolateral prefrontal region ('F3', 'F4')	**Interhemispheric cross-coherence during EEG**	Desynchronization over the right prefrontal, premotor, sensorimotor area (electrodes 'F10', 'FC6' and 'C2' predicted clinical improvement on the UPDRS III p = 0.002	-	-
NEUROIMAGING							
Dong 2020 [52]	fMRI	OFF	Executive Control Network (ECN)	**Functional connectivity**	ECN ↓ p<0.001	-	-
Ge 2020	FDG-PET	°FF	PDRP areas: thalamus, putamen, GPi, caudate	**Local and global metabolic**	PDRP levels↑ p = 0.039	PDRP levels↑	-

[53]			nucleus, sensorimotor cortex, cerebellar vermis, precuneus, pons	**activity**		p = 0.094	
Hanssen 2019 [54]	Resting state fMRI	1) ON 2) OFF	Ganglia-thalamo-cortical circuit; Cerebello-thalamo-cortical circuit	**Effective connectivity**	ON state: ↑ p<0.001 OFF state: ↑p<0.005	-	-
Hilker 2004 [55]	FDG-PET	1) ON 2) OFF	Associative and limbic cortices; cerebellum	**Metabolic activity**	ON state: ↑ p<0.001 OFF state: ↓ p<0.001	-	-
Hilker 2005 [56]	F-DOPA-PET	ON	Caudate nucleus and putamen	**Striatal F-dopa uptake**	F-dopa uptake ↓ in putamen (p<0.05) and caudate nucleus (p<0.01)	-	-
Lokkegaard 2007 [57]	[123I] FP-CIT SPECT	ON	Striatum	**Dopamine transporter binding**	No differences between groups	No differences between groups	-
Mubeen 2018 [58]	PET	1) ON 2) OFF	Whole brain	**Cerebral blood flow**	ON state: ↑ p<0.001 OFF state: ↓ p = 0.029	-	-
O'Gorman Tuura 2018 [59]	MRS	OFF	Basal ganglia (GABA and Glu) and pons (Glu)	**Gaba and Glutamate activity**	↑ GABA p = 0.009 ↓ Glu pons p = 0.049	-	-

Palard-Novello 2020 [60]	FDG-PET	ON	Limbic and associative cortices	**Metabolic activity**	↓ activity of frontal cortex (BA 6 and 9) p<0.05 ↑ frontal cortex (BA 39 and 17) P<0.05	-	-
Peron 2010 [61]	FDG-PET	ON	ToM areas: limbic circuit, associative cortex and cerebellum	**Metabolic activity**	↓activity cingulate and frontal gyrus, p<0.001; ↑ activity of cerebellum and inferior parietal lobule, p<0.001	-	-
Sidtis 2012 [62]	PET	1) ON 2) OFF	Whole brain	**Cerebral Blood Flow**	ON state: ↑ p<0.001	-	-
Smith 2019 [63]	FDG-PET	ON	Basal ganglia, associative cortices and cerebellum	**VMAT 2 and glucose metabolism**	↓ VMAT 2 in striatum p<0.05 ↓ glucose metabolism in striatum ↑ glucose metabolism in parietal, temporal cortices and cerebellum p < 0.05	-	-
Vassal	DTI-FT	ON	VTA connectivity with	**Brain**	↑ VTA connectivity	-	-

2019 [64]	cortical areas and cerebellum	**Connectivity**	with: brainstem, cerebellum, premotor and motor cortex

↑ (increased); ↓ (decreased); MER (Multi-pass microelectrode recording); TMS (Transcranial Magnetic Resonance); LFPs (Local Field Potentials); ERNA (Evoked Resonant Neural Activity); EEG (Electroencephalography); MEG (Magnetoencephalography); VEPs (Visual Evoked Potentials); SEPs (Somatosensory Evoked Potentials); STN (Subthalamic nucleus); RAS (Rhythmic auditory stimulation); FDG-PET (Fluorodeoxyglucose-Positron Emission Tomography); fMRI (functional Magnetic Resonance Imaging); [123I] FP-CIT SPECT (Single-photon emission computed tomography with [123I] FP-CIT ([123I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane); MRS (Magnetic Resonance Spectroscopy); DTI-FT (Diffusion Tensor Imaging-fiber tracking); PDRP (Parkinson's Disease Related Pattern); ToM areas (Theory of Mind areas); VMAT 2 (vesicular monoamine transporter 2); VTA (Ventral Tegmental Area)

3. Quality Assessment

Due to the nature of the included studies, no standardized checklists were applicable for the appraisal of the methodological quality. However, a set of predefined key qualitative elements that represented the methodological quality of the studies was established. Specifically, when assessing the selection bias, we considered how patients with PD and controls were enrolled, including the diagnostic criteria (Table 1). Diagnostic criteria and other clinical data, such as surgical criteria or Unified Parkinson's Disease Rating Scale (UPDRS) score, were also collected to characterize the study population and observe if any clinical information was relevant in explaining DBS outcomes. On the other hand, when assessing the appropriateness of the measurement of exposure, we considered the criteria applied for referring patients to DBS and the criteria for the assessment of the appropriateness of biomarker measurement (methods of sample collection, handling, storage, and analysis) (Table 2a, Table 2b). Moreover, since the disease-modifying outcomes are strictly linked with time, the time from surgery to biomarker assessment was also considered ("follow-up", Table 1) to evaluate if the length and the number of follow-ups were consistent with the biological plausibility.

4. Results

The bibliographic search yielded 2,960 records. A total of 75 studies were initially selected. Six duplicates were removed, and the remaining 69 studies were assessed for inclusion in the study. Later, 26 studies were excluded because they did not meet the predefined inclusion criteria. Finally, 43 studies were included for the data extraction. The process of study selection is presented in Figure 1.

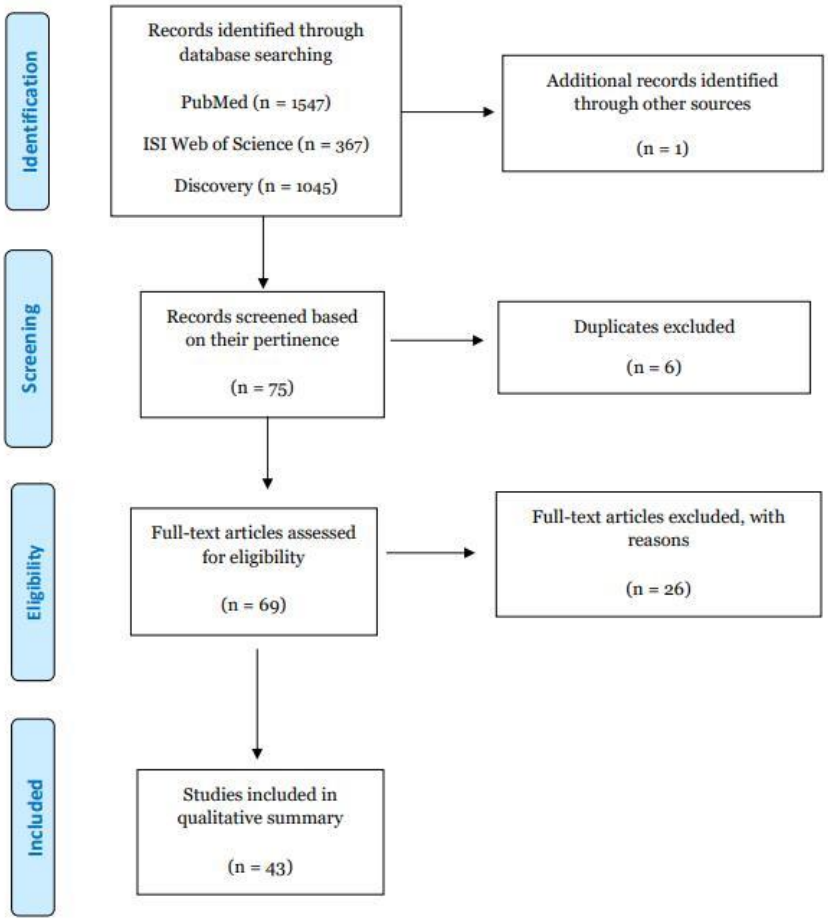

Figure 1 PRISMA flowchart describing the inclusion and exclusion of the articles

The included articles were divided into three main categories depending on the nature of DBS outcomes examined in the study: biochemical (12 studies), epigenetic (4 studies), and neurophysiological (27 studies: 14 electrophysiological and 13 neuroimaging studies).

Overall, the included studies were of moderate to low quality. As described more thoroughly in the next section, the diagnostic and surgical criteria adopted within the included studies were widely heterogeneous, and in several cases, were either not reported or not specified. Most of the studies had a small sample size and thus had limited statistical power. Moreover, examined biomarkers and analytical methods were highly heterogeneous.

4.1 Characteristics of the Included Studies

4.1.1 Sample Size

A total of 20 out of 43 studies (46.5%) examined the effects of DBS on patients with PD without a control group. Seven of these studies had a sample size of ≤10 patients, with a mean sample size of 8.3 patients. The remaining thirteen studies had enrolled a mean of 17.4 patients, with only five studies [25, 51, 54, 56, 60] enrolling ≥20 participants (the highest number of participants was 32).

The twenty-three studies that also had a control group enrolled a mean of 17 (the highest number of cases was 60) patients with PD (cases) and 18.5 controls (the highest number of

controls was 156). Only five studies [29, 39, 42, 45, 57] also included patients with PD in the control group, whereas the remaining eighteen studies enrolled healthy controls (HC).

4.1.2 Mean Age and Gender Distribution of the Participants

The mean age of the participants enrolled in the studies ranged from 51 to 80 years in the cases and 57 to 77 years in the controls, with 20 studies (46.5%) recruiting PD patients with a mean age of ≤60 years and no study enrolling participants aged ≤50 years.

Twenty-eight studies (65.1%) recruited a higher number of male cases (mean: 10.5 males, 5.2 females). Seven studies [28, 29, 45-47, 54, 57] did not specify the male/female ratio. Twelve studies out of 23 (52.1%) recruited more males in the control group (mean: 7.3 males, 3.6 females), while four studies [28, 29, 39, 45] did not report the gender proportion.

4.1.3 Diagnostic Criteria for PD

Eleven studies [22, 26–28, 31, 53, 55, 56, 60, 61, 63] used the "UK Parkinson's disease Brain Bank criteria" [65] for the diagnosis of idiopathic PD, four studies [41, 43, 45, 46] adopted the "Hoehn and Yahr scale" [66], and two studies [24, 54] used the "Movement Disorder Society criteria" [67]. However, most of the studies (55.8%) did not specify the adopted criteria and only reported that the cases had a neurological history of idiopathic PD.

4.1.4 Surgical Criteria

Twenty-eight studies (65.1%) did not specify the surgical criteria that were adopted to select the patients with PD that could undergo DBS surgery. Four studies [45, 56, 57, 63] adopted the "CAPSIT criteria", while three studies [43, 46, 51] used the "Hoehn and Yahr scale". However, most studies specified that PD patients that had undergone DBS surgery were refractory to medical treatment.

4.1.5 Pharmacological Treatments

L-DOPA was the main pharmacological treatment used to manage the motor symptoms in patients with PD (Table 1). The mean dose ranged from 300 mg to 2000 mg per day. Treatment was often suspended before surgery and the washout period lasted from 8 to 72 h. Only in three studies [39, 42, 57] did the controls also receive an antiparkinsonian treatment. In the study by Michmizos et al. [45], although the cases and controls were diagnosed with PD, the pharmacological treatment was not described.

4.1.6 UPDRS Score before Surgery

Twenty-eight studies (65.1%) reported the UPDRS score at baseline before the surgery. The mean UPDRS score in the OFF phase (without pharmacological treatment) ranged from 17 to 74. Eighteen studies (64.2%) reported a score of ≥42, indicating severe PD. Only in three studies by Soreq et al. [34–36] was the baseline UPDRS score <30, thus indicating moderate PD. Two studies by Anidi and Michmizos [39, 45] were the only studies that assessed the UPDRS scale in the control group, with scores of 35.7 and 59.4, respectively.

4.1.7 UPDRS Score after DBS

Twenty-five studies (58.1%) reported the UPDRS score after surgery in the cases. Only eleven studies assessed the UPDRS scale in the OFF phase (without stimulation), reporting a mean score ranging from 27.4 to 54.6. Only one [53] study reported a UPDRS score of <30, with a progressive increase nine months after surgery (mean score = 49.3 ±18.2). Sixteen studies reported a mean UPDRS score in the ON phase (with DBS stimulation) ranging from 9.2 to 37.6, with nine of them (56.2%) reporting a score of ≤20. Four studies [47, 50, 54, 57] did not specify the UPDRS score but only reported an increase or a decrease in the score.

4.1.8 Location of Implanted DBS

In all the studies except one [60], the electrodes were inserted bilaterally in the STN. Only in the study by Palard-Novello et al. [60] were the electrodes inserted bilaterally in the GPi. In one study [46], four patients were implanted with a bilateral GPi-DBS and two with a bilateral STN-DBS. In another study [32], seven patients had a history of bilateral stimulation in the STN, one patient had unilateral STN stimulation, while two patients had bilateral GPi stimulation, and one patient had unilateral GPi stimulation. In one study [24], the location of the electrodes was not specified. Only in three studies [39, 42, 45] was the control group also treated with DBS.

4.1.9 Follow-Ups

In 20 out of 43 studies (46.5%), the participants were observed before DBS and after several months after surgery. The mean duration of follow-up after DBS surgery ranged from 1 month to 11 years. However, only Constantinescu et al. [23] reported a follow-up of 11 years, while 26 out of 43 studies (60.4%) followed up the participants for only ≤1 year.

Eleven studies (26.8%) enrolled patients with PD that had already received an implant and had been treated with DBS for at least 1 year.

Four post-mortem studies [28, 29, 30, 32] examined the brain tissue of patients with PD who had been treated with DBS for a mean of five years until death.

Moreover, 14 out of 43 studies (32.5%) followed up with participants at least twice after DBS, whereas the remaining 29 studies (67.4%) observed patients once after DBS, with most being neurophysiological studies (75.9%). On the other hand, five biochemical [22, 23, 25, 31, 33] and all the epigenetic studies followed-up participants at least twice after the surgical procedure.

4.2 Biochemical Studies

We included twelve studies that assessed the biochemical changes in PD patients that had undergone DBS treatment to explore if the surgery modified the progression of PD by changing the biochemical patterns.

As described in the introduction, one of the main biochemical hallmarks of PD is the aggregation of Lewy bodies composed of α-synuclein. However, only one study [29] investigated the changes in α-synuclein after exposure to DBS. That study had focused on the post-mortem brain tissue of patients with PD by assessing α-synuclein and SN neurons. The authors did not observe significant results suggesting a potential disease-modifying effect of surgery. Rather, they

showed an increase in the density of α-synuclein after DBS, suggesting a progression of the disease.

In contrast, three other post-mortem studies [28, 30, 32] reported a significant effect of DBS on the brain of treated participants compared to those who did not receive DBS and HC. The studies focused on different biomarkers, such as the mean distance and mitochondrial volume of dopaminergic synapses in the striatum [28], Vascular Endothelial Growth Factor (VEGF) [64], and Proliferating Cell Nuclear Antigen antibody (PCNA) in the sub-ventricular zone (SVZ) [31]. Overall, the results of these studies indicated a remarkable neuroprotective action of DBS through neurotrophic mechanisms.

Moreover, since tau proteins and brain amyloidosis (Aβ-42) are important markers of neurodegenerative processes, one study [23] investigated the potential association between the levels of cerebrospinal fluid (CSF) and the exposure to DBS. Those authors did not find any significant results throughout the follow-up, suggesting that DBS might have a minimal effect on these neurodegenerative mechanisms.

On the other hand, the study by Wang et al. [33] reported an interesting result on the potential disease-modifying effect of DBS. The authors found a link between tetranectin and STN stimulation. Since tetranectin is involved in the degradation of proteins in the brain, the authors suggested that elevated tetranectin levels following STN-DBS could be linked to a reduction in the aggregation of abnormal proteins and neurodegenerative processes [33].

Neurodegeneration in PD also includes chronic inflammation processes and oxidative stress, which are related to a dysregulation in the homeostasis of iron metabolism [68]. Based on this, two studies [26, 27] assessed the pre-and post-DBS levels of two proteins (pro-hepcidin and hepcidin) involved in iron metabolism and a protein linked to anti-inflammatory processes (interleukin-6), reporting an unclear link between these proteins and DBS.

The remaining four studies [22, 24, 25, 31] investigated the efficacy of DBS by assessing several biomarkers, including HPA (Hypothalamic-pituitary-adrenal) axis markers [31] and urinary levels of catecholamines [25], but they did not find any significant results supporting a disease-modifying effect.

4.3 Epigenetic Studies

We included four epigenetic studies by Soreq and colleagues [34–37]. In all the included trials, blood samples were collected to analyze leukocytes, adopting the same study design. However, none of these studies examined potential disease-modifying effects. The authors were initially interested in investigating any relations between molecular changes and reversible motor improvements induced by STN-DBS. The authors focused on different epigenetic biomarkers potentially involved in PD, such as transcript isoforms [34], miRNAs [35], alternative splicing (AS) events [36], and long non-coding RNA (lncRNA) [37]. In all these studies, Soreq and colleagues reported significant but transient modifications of the biomarkers in participants treated with DBS in the ON phase, suggesting that surgery may only have a reversible effect on PD symptoms. However, the potential utility of these markers in assessing the biological effects of DBS in patients with PD should be further explored, as they have been found in peripheral biofluids (saliva, blood, plasma, serum, and urine) and are thus easy to obtain with no substantial health risks.

4.4 Neurophysiological Studies

4.4.1 Electrophysiological Studies

Parkinsonian aberrations such as rigidity have also been correlated with impairments in beta oscillations [40]. Therefore, it is important to explore changes in the beta activity, as markers of potentially relevant effects of DBS on the pathophysiology of PD. We included six electrophysiological studies [39, 42, 45, 47, 48, 50] that investigated Local Field Potentials (LFPs) focusing on beta burst activity. None of these studies found significant results suggesting a potential disease-modifying effect of DBS. Giannicola et al. [42] investigated potential disease-modifying patterns but did not observe any differences in the beta activity between acute and hyper-chronic patients with PD treated with DBS. Other studies reported only a temporary beneficial effect on the beta activity, pointing out that a decrease in the beta burst activity was associated with improved motor symptoms in patients with PD [39, 43, 45, 47, 50, 51].

The remaining studies [38, 40, 41, 44, 46, 49] examined different cortical regions and waves, reporting only transient positive effects on motor symptoms after stimulation.

4.4.2 Neuroimaging Studies

The use of neuroimaging techniques such as PET or MRI is an accessible method to measure the efficacy of DBS and identify the possible physiological changes in the brain of treated patients.

Most of the neuroimaging studies included in this review had explored different cerebral pathways to assess a potential neurophysiological effect of DBS. Four studies [53, 56, 57, 63] investigated the potential of DBS to affect the progression of the disease through possible neuroprotective effects. None of these studies reported any significant results. Lokkegaard et al. [57] compared patients that had undergone DBS to those that were only treated with pharmacological intervention, and observed a decrease in the binding of dopamine transporters in the striatum before and after intervention in both groups, suggesting a nigrostriatal neuronal degeneration.

Two further studies [53, 56] investigated a potential disease-modifying effect of DBS but did not report any significant results. Ge et al. [53] examined PD-related metabolic covariance patterns (PDRP) after STN-DBS surgery but did not find any significant differences at 12 months of follow-up compared to baseline. Hilker et al. [56], found a significant decrease in the uptake of striatal 18F-dopa in PD subjects, thus revealing a decline in dopaminergic function even in PD subjects that were effectively treated with STN stimulation.

On the other hand, one study [63] observed a correlation between the clinical outcomes, specifically an improvement in tremor and depressive symptoms, along with a decrease in VMAT2 (vesicular monoamine transporter 2) in the striatum, associative striatum, and extra-striatum. Since a decrease in VMAT2 has been associated with increased dopamine [70], the authors proposed that DBS might be related to an increase in dopaminergic activity. However, this study followed up PD patients only once after DBS; thus, the authors were not able to report other relevant results during the subsequent months.

The remaining nine studies [52, 54, 55, 58–60, 61, 62, 64] also investigated several biomarkers but did not report any potential disease-modifying effect. However, two studies [54, 59] examined different biological aspects and reported some interesting findings. One study [54] suggested that

the improvements induced by DBS in PD symptoms could be due to an interaction between the cerebellum and the putamen, while the second study [59] suggested that pontine glutamine (Glx) and basal ganglia Glutamate (Glu) levels were potentially significant predictors of the efficacy of DBS, indicating a role of glutamatergic neurotransmission in the therapeutic mechanism of DBS.

5. Discussion

In this systematic review, we summarized the available evidence on several biological and physiological processes that were associated with DBS in human participants with PD. The main objective was to understand if these processes could be connected to a potential disease-modifying effect.

Only three studies [28, 30, 32] reported significant results, suggesting a potential disease-modifying effect of DBS. All these studies examined post-mortem brain tissue. Specifically, Mallach et al. [28] reported that DBS might have a role in inhibiting or reversing the decrease in mitochondrial volume, as well as the number of dopaminergic striatal neurons, caused by disease progression. The authors explained that this could be associated with the possible effect of DBS in inhibiting STN, which would subsequently inhibit the glutamate excitotoxicity in the SNpc [28]. Furthermore, the possible long-term consequences of decreased glutamate excitotoxicity would be the loss of calcium-dependent mitochondrial fragmentation, increased mitochondrial volume, and decreased neuronal death [28].

Furthermore, Pienaar et al. [30] suggested an association between STN-DBS and an improvement of microvascular markers. The authors observed a dramatic increase in VEGF, a neurotrophic protein produced by vascular endothelial cells, which may stimulate vasculogenesis and angiogenesis. Therefore, these results indicated that STN-DBS could reverse the extent of vascular pathology in PD by stimulating the survival, proliferation, and migration of vascular endothelial cells. The third study [32] reported an effect of DBS in increasing the cellular plasticity in the brain, suggesting that the effects of surgery might affect a wider area than that directly surrounding the location of the electrode. The authors observed a higher number of SVZ precursor cells (lateral ventricle and third ventricle) in the brains of patients who had undergone DBS compared to those of healthy controls and subjects who did not undergo surgery. The results revealed an increased proliferation of neural precursor cells in the brains of human participants after DBS surgery and electrical stimulation [32]. These results were consistent with those obtained from a study that suggested that STN-DBS might cause a neurotrophic mechanism of neuroprotection by specifically increasing the levels of BDNF [17]. According to this hypothesis, the release of BDNF could be induced by electrical stimulation, thus explaining why high-frequency stimulation in neuronal cultures appeared to cause an increase in the release of BDNF [71]. All these studies were conducted using small sample sizes; thus, despite reporting some significant results, the studies were not strong enough to support a significant effect of DBS in preventing the progression of PD.

Moreover, the study by Wang et al. [33] reported a potential neuroprotective effect of DBS in patients with PD. The authors suggested that tetranectin could be involved in this mechanism by increasing the levels of dopamine and decreasing the accumulation of abnormal proteins. Similarly, a previous study by Wang et al. [72] reported reduced levels of tetranectin in patients with PD compared to HC, with further evidence suggesting a role of this protein in the degradation

of misfolded proteins [73]. Thus, the observation of higher levels of tetranectin after DBS could suggest the neuroprotective effect of surgery. However, the exact role of this protein in PD has not yet been clarified, and further studies are required.

However, most of the included studies did not support the disease-modifying hypothesis. Particularly, three studies [29, 42, 57] compared participants that had undergone DBS with those that were only pharmacologically treated and reported no differences between the two groups in terms of disease progression. Only a few studies [29, 56, 57, 63] have investigated the typical pathobiological and pathophysiological hallmarks of PD. As mentioned before, the typical hallmarks of PD are often associated with the aggregation of α-synuclein and dopaminergic degeneration in SNpc and other basal ganglia structures [74]. However, most of the included studies examined different biological and physiological biomarkers. Overall, the biological and neurophysiological aspects covered by the included studies were highly heterogeneous. Few studies focused on similar biological and neurophysiological aspects. For example, the included neurophysiological studies adopted the same procedures (such as PET and MER) but examined different neurophysiological aspects and pathways. Similarly, although the four epigenetic studies had the same study design and population, they investigated different epigenetic variables. This heterogeneity in the biological and physiological aspects prevented a direct comparison of studies and limited the reliability of the results in suggesting any significant disease-modifying effect associated with DBS.

A further limitation of the reliability of results in suggesting a potential disease-modifying effect of DBS was that 60.4% of the studies had a follow-up of ≤1 year, while 67.4% of the studies observed patients only once after DBS.

Overall, our review reports a significant effect of STN-DBS only during the ON phase, thus suggesting that the effect might be limited and transient. Some of the included neurophysiological studies have reported that the observed metabolic and physiological changes almost completely disappeared during the OFF phase, again indicating the functional and temporary effects of DBS, consistent with the relapse of severe Parkinsonism in the OFF phase of DBS. Moreover, substantial improvements in the UPDRS scores were observed after surgery, only during the ON phase.

However, it is worth highlighting that, although 55.8% of the studies did not specify the adopted diagnostic criteria, most of them observed late-stage patients with PD about ten years after diagnosis. The recruitment of late-stage patients with PD could be another factor that may partially explain the lack of significant results suggesting a potential disease-modifying effect of DBS. Most of the loss of putaminal denervation occurs within four years after the diagnosis [75]. Thus, assessment of a potential disease-modifying effect in a PD patient in whom the dopaminergic striatal innervation has been lost long back might be inappropriate [76].

Dysfunction and degeneration of the nigrostriatal system begin long before the diagnosis of PD. It has been estimated that, by the time of onset of motor symptoms and subsequent diagnosis, the patients have already lost half of the striatal dopamine content, along with 30% of the nigral dopamine neurons [75]. A study by Kordower and colleagues [76] demonstrated that patients reached the diagnosis stage when 50% of the putaminal denervation had already occurred and that this denervation progressed to an approximately 90% loss within four years after diagnosis. These results suggest that enrolling a population with an advanced stage of the disease might be inappropriate when investigating the potential neuroprotective effects of specific interventions [76]. Several preclinical studies support a potential disease-modifying effect of DBS. Some studies

on rats have reported that the use of STN-DBS immediately after the administration of 6-hydroxydopamine (6-OHDA) doubled the number of remaining tyrosine hydroxylase immuno-reactive neurons in the SNpc [77], and the activation of STN-DBS at 1 or 2 weeks after the administration of 6-OHDA protected the remaining SNpc neurons from further degeneration [78, 79]. Similar results were observed in primate models of PD using STN-DBS just before or six days after the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [16].

These findings suggest that to explore the potential disease-modifying effects of DBS, studies should enroll patients with milder symptoms and whose neural circuitry and physiology may still respond to DBS. Based on these criteria, a study [80] reported that DBS was superior to medical therapy alone during early-stage PD, before the appearance of severely debilitating motor complications, suggesting that neurostimulation may be a potential therapy for patients in an early stage of the disease. It must be highlighted that DBS is expensive compared to conventional medical therapy, which, apart from being a non-invasive intervention, facilitates an excellent control of symptoms [81]. However, available evidence on the long-term benefits of DBS is insufficient to support the initiation of DBS at an early stage of the disease. Moreover, despite significant technological progress, stereotactic surgery still has a combined risk of permanent morbidity or mortality of 1–3%, depending on the surgical center and caseload volume [81]. However, as observed in some of the included articles, DBS has been shown to cause substantial improvements in the health-related quality of life, as well as maintain the improvements in symptoms [82]. Moreover, considering that the risks related to surgery are lower in younger subjects with lower brain atrophy and fewer comorbidities, as well as the fact that younger patients have been reported to benefit the most from the intervention [83], DBS might be considered as a feasible treatment option at an earlier stage of the disease.

Due to several limitations of the included literature, the obtained evidence was inconclusive in identifying a potential disease-modifying effect of DBS. Nevertheless, three post-mortem studies have suggested a potential neuroprotective effect of DBS, which justifies further high-quality epidemiological studies enrolling a larger number of subjects to assess if and how this surgical procedure can modify the course of the disease. Specifically, studies should adopt a more suitable design, focusing on the appropriate selection and recruitment of participants based on homogeneous, validated, and standardized diagnostic criteria, as well as adopting an adequate duration of follow-up, including a sufficient number of observations.

Currently available preclinical literature suggests that STN-DBS could mediate neuroprotection at an early stage of the disease. Based on this premise, carrying out further prospective clinical trials examining the course of PD in early-stage patients could be useful.

Further research should focus on expanding our understanding of the biological and physiological changes in the brain caused by either disease progression or chronic electrical stimulation. Current research on the biological and neurophysiological aspects involved in DBS is still widely heterogeneous. Therefore, it could be crucial to reach a consensus on the most appropriate and reliable biomarkers to assess the efficacy of DBS.

Since PD is a highly complex disease, it is unlikely that a single biomarker will be sufficient. Rather, a panel of established and standardized biomarkers covering a range of metabolic and physiologic processes, including genetic, neuroimaging, and metabolic markers, would be helpful.

We believe that such a result could be useful in supporting neurosurgeons and neurologists in assessing the efficacy of DBS, both in clinical practice and in a research setting.

6. Conclusions

This paper aimed at systematically reviewing the biological and physiological effects of DBS in human patients with PD, focusing on its potential disease-modifying features. The reviewed studies investigated a set of widely heterogeneous and complex biological and neurophysiological aspects, and only a few studies specifically investigated the potential neuroprotective and disease-modifying effects of DBS. Most of the included studies did not support the disease-modifying hypothesis, showing transient biological and neurophysiological effects. All the included studies had some methodological limitations, mostly related to study design and patient recruitment. We believe that identifying a panel of common biomarkers and criteria might be crucial to characterize the features of PD better and assess the potential of DBS to modify the course of the disease.

Author Contributions

F.S.: data collection and analysis, writing of the manuscript. G.R.: data collection, drafting of the manuscript. L.T.: data collection, drafting of the manuscript. G.S.: data collection. F.T.: data collection. G.R.: data collection. E.L.: methodology, drafting of the manuscript. M.C. (Massimo Corbo): revising the manuscript critically for important intellectual content. M.C. (Marco Canevelli): drafting and revising of the manuscript. N.V.: conception of the study, revising of the manuscript. P.P.: data collection, drafting and revising of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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