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Deep Brain Stimulation Impact on Voice and Speech Quality in Parkinson's Disease: A Systematic Review

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Abstract

Objective. Deep brain stimulation (DBS) has considerable efficacy for the motor dysfunction of idiopathic Parkinson's disease (PD) on patient quality of life. However, the benefit of DBS on voice and speech quality remains controversial. We carried out a systematic review to understand the influence of DBS on parkinsonian dysphonia and dysarthria.

Data Sources. A PubMed/MEDLINE and Cochrane systematic review was carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Population, Intervention, Comparison, Outcome, Timing, and Setting (PICOTS) statements.

Review Methods. Three investigators screened studies published in the literature from inception to May 2022. The following data were retrieved: age, demographic, sex, disease duration, DBS duration, DBS location, speech, and voice quality measurements.

Results. From the 180 studies identified, 44 publications met the inclusion criteria, accounting for 866 patients. Twenty-nine studies focused on voice/speech quality in subthalamic DBS patients, and 6 included patients with stimulation of pallidal, thalamic, and zona incerta regions. Most studies (4/6) reported a deterioration of the vocal parameters on subjective voice quality evaluation. For speech, the findings were more contrasted. There was an important heterogeneity between studies regarding the voice and speech quality outcomes used to evaluate the impact of DBS on voice/speech quality.

Conclusion. The impact of DBS on voice and speech quality significantly varies between studies. The stimulated anatomical region may have a significant role since the stimulation of the pallidal area was mainly associated with voice quality improvement, in contrast with other regions. Future controlled studies comparing all region stimulation are needed to get reliable findings.

Level of Evidence. Level III: evidence from evidence summaries developed from systematic reviews

Keywords

Parkinson's disease, dysarthria, speech performance, voice, deep brain stimulation

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The destruction of the dopaminergic neurons of the substantia nigra is characterized as idiopathic Parkinson's disease (PD). PD, the second most frequent neurodegenerative disease in the United States in 2017,[1] is characterized by massive dopaminergic neuronal loss associated with extensive Lewy pathology, which is the second most frequent neurodegenerative disease. Disorders are clinically divided into a triad of motor symptoms—akinesia, plastic hypertonicity, and resting tremors[2]—and nonmotor symptoms,[3] the latter of which have long been underestimated but are nevertheless a source of serious disability. Dysphonia is prevalent in PD, being found between 70% and 90% of patients.[4] Dysarthria is described as hypokinetic and concerns up to 90% of patients.[5,6] Patients often have reduced voice pitch, voice tremor, and low speech, punctuated by sudden acceleration and syllabic repetitions (palilalia). Intelligibility is compromised, leading to an important impact on quality of life.[7] PD therapies aim to increase levels of available dopamine.[2] Medical treatments are effective only on the motor symptoms, and they do not slow the degeneration of the dopaminergic neurons. The duration of the treatment efficacy decreases over time, leading to a new therapeutic strategy.[2] One of the final therapies for PD patients is deep brain stimulation (DBS), and its impact on speech and voice quality is still controversial.

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High-frequency deep brain stimulation was first described in 1987 and proved to be highly effective for the treatment of motor symptoms in PD patients.[8] Mechanisms underlying the beneficial effects of DBS are poorly understood and remain controversial. DBS reverses (or disrupts) pathological oscillations in the basal ganglia network observed in PD patients.[9] DBS is most often applied in the subthalamic nucleus (STN) with global efficacy and can also be applied at the level of the thalamic ventral intermediate nucleus (VIM), acting mainly on tremor in this location. The pallidum can also be stimulated to provide greater reduction of dyskinesias but with variability depending on the exact location of the stimulation within this structure.[8] To date, the impact of DBS on voice and speech performance has been poorly investigated and remains unclear. Conflicting results have been reported since DBS may result in improvement, as part of its overall efficacy, but may also been associated with no effect or even worsening.[10]

The objective of this systematic review is to determine the extent to which DBS improves, worsens, or has a neutral effect on voice and speech in PD patients.

Methods

The criteria for consideration of study inclusion were based on the Population, Intervention, Comparison, Outcome, Timing, and Setting (PICOTS) framework.[11] Three authors (R.B., L.C., J.R.L.) independently reviewed and extracted data of studies regarding the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[12]

Eligibility Criteria

Randomized controlled trials and observational studies published in the literature without any language restrictions from inception to May 2022 were included in this systematic review. Studies were included if they reported voice or speech quality outcomes of patients who benefited from DBS. Only studies reporting data for more than 10 individuals were considered.

Populations and Inclusion/Exclusion Criteria

The controlled and uncontrolled prospective or retrospective studies specifically reporting data on voice quality (VQ) or speech quality (SQ) after DBS were included. To be included, authors had to report subjective or objective changes in VQ and SQ from pre- to post-DBS stimulation. Case reports, experimental studies in animals or nonliving animals, and studies in which DBS was applied to other neurodegenerative diseases were excluded. Authors investigated the study design, the number of patients, the sex ratio, the mean or median age, and the PD duration since diagnosis.

VQ and SQ Evaluation

The data reporting the effects of DBS on parkinsonian VQ and SQ were noted. Subjective and/or objective VQ (subjective: Voice Handicap Index (VHI), Grade, Roughness, Breathiness, Aesthenia, Strain, (Intensity) GRABAS(I), Assessment of Motor Speech Disorders (AMSD); objective: F0, F2, jitter, and shimmer) and SQ (subjective: Sentence Intelligibility Test [SIT], vowel articulation; objective: fluency [words/min], verbal production, vocalic transition, and prolonged phonation) evaluations and the methods of measurement on different speech materials (spontaneous and/or read phonetic text) were noticed. The effects of DBS at the STN, the VIM, and the pallidum were considered. For each stimulation site, we sought to determine whether the data tended to demonstrate an improvement, a worsening, or no effect on dysarthria. Then, in the event of worsening or onset of dysarthria under DBS, we researched how to explain and prevent this adverse effect. Studies were classified according to their level of evidence according to the adapted version of Sackett's classification (I-V).[13,14]

Intervention and Comparison

The following surgical approaches were considered: subthalamic, thalamic, pallidal, and zona incerta DBS. If informed, the influence of speech therapy was noted.

Timing and Setting

There were no criteria for specific stage or timing in the ''disease process'' of the included population.

Search Strategy

The publication search was conducted with PubMed/MEDLINE and Cochrane databases. The databases were screened for abstracts and titles referring to the description of outcomes of patients benefiting from DBS. Three authors analyzed full texts of selected studies (R.B., L.C., J.R.L.). Results of the search strategy were reviewed for relevance, and the reference lists of these publications were examined for additional pertinent studies. There were no discrepancies in synthesized data among the 2 authors. The following keywords were included: ''Parkinson's disease,'' ''Dysarthria,'' ''Speech performance,'' ''Voice,'' ''Deep Brain Stimulation or DBS.''

Bias Analysis

We conducted an analysis of cofactors that may interfere with the comparison of included studies using the Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group (McMaster University, Ontario, Canada) and the Agency for Healthcare Research and Quality.[15] The bias analysis consisted of evaluation of cofactors that may affect the comparison of studies (ie, epidemiological, clinical, outcome evaluations, DBS surgical and brain region features). Due to heterogeneity in outcomes reporting, no quantitative analysis (ie, meta-analysis) was performed.

Results

From the 180 studies identified on PubMed/MEDLINE and Cochrane without time restriction, 44 articles published between 2000 and 2022 were included (**Table 1**), representing 866 patients. The flowchart is available in **Figure 1**. Two studies included results of endoscopic clinical observations (insufficient glottal closure under DBS),[16,17] and 3 included a videostroboscopic examination.[18-20] Within the time constraints of the analysis, 2 studies evaluated the efficacy of

Table 1. Literature Search Strategy.[a]

Search	No. of results
PubMed/MEDLINE	
#1. (Dysarthria) OR (Speech performance)	40,129
#2. #1 AND (Parkinson's disease)	1218
#3. #2 AND ((Deep Brain Stimulation) OR (DBS))	199
#4. #3 limited to humans	170
Selected publications	44
Cochrane	
(Dysarthria) OR (Speech performance) AND (Parkinson's disease) AND (Deep Brain Stimulation) OR (DBS)	10
Selected publications	0

[a]Algorithm applied on May 30, 2022.

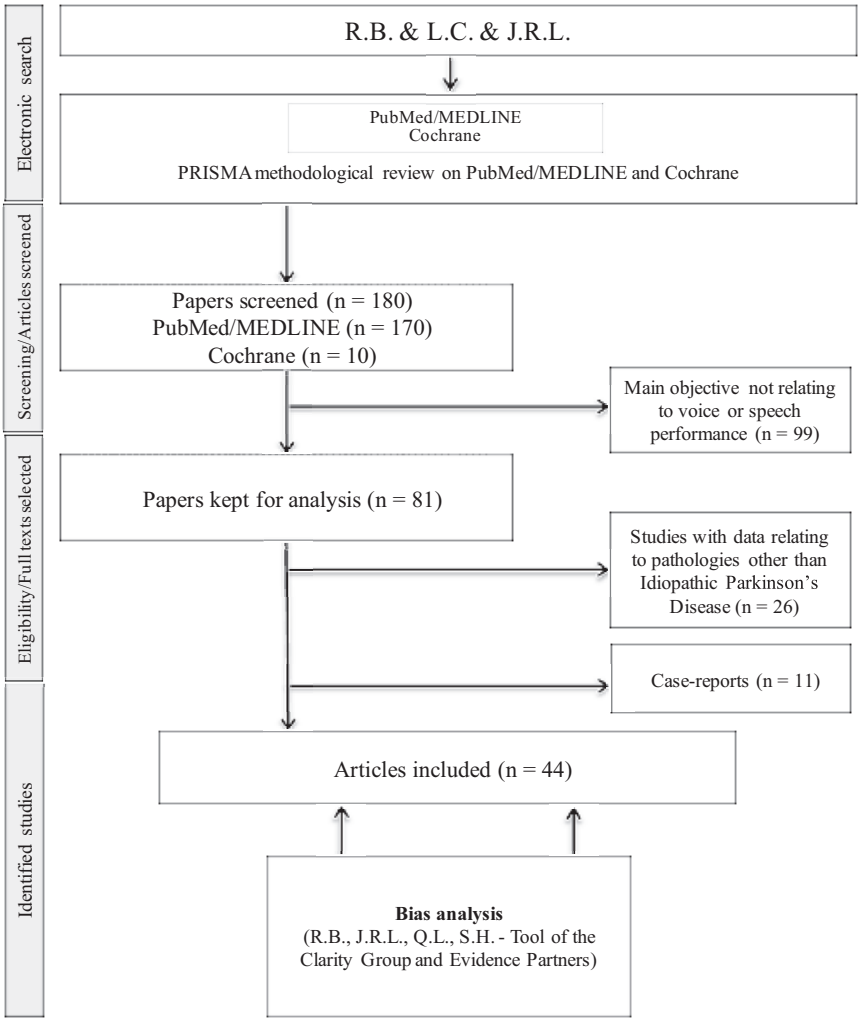

Figure 1. Flowchart. Systematic review of the effects of deep brain stimulation on voice and speech in idiopathic Parkinson's disease, between 2011 and 2021, conducted with PRISMA methodology. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

vocal rehabilitation using the Lee Silverman voice treatment (LSVT) method[21,22] for this indication, but only on a very small number of patients (10 and 4 patients in the LSVT group, respectively, with DBS) and with contradictory results.

Location of the DBS

Twenty-nine studies were devoted to speech disorders following the establishment of a subthalamic DBS (see Supplemental Material 1 in the online version of the article), and 6 were

devoted to stimulation of other sites: pallidal (2), thalamic (VIM) (2), and zona incerta (2) (see Supplemental Material 2 in the online version of the article), with 3 of them including patients with subthalamic DBS for comparison.

Voice and Speech Quality Outcomes

Voice and speech quality measurements are synthetized in **Table 2**. A large heterogeneity concerning the effects of STN-DBS on voice and speech performance was found. Twelve studies were devoted to the amelioration or prevention of stimulus-induced speech disorders in PD (**Table 3**). Most studies evaluated the feasibility and efficacy of modifying stimulation parameters to prevent voice deterioration with DBS. Those studies reported on frequency modulation,[23,24] duration of the stimulation pulses,[25] interleaving stimulation,[26] and adaptive stimulation.[27]

Bias Analysis

Most studies accounted for age difference and motor impairment Unified Parkinson Disease Rating Scale III (UPDRS-III)[28] but lacked specificity about voice-threatening comorbidities or cognitive impairment Mini-Mental State Examination (MMSE),[29] leaving some doubt about a selection bias. Duration of DBS was incorporated into the study design and did not emerge as a confounding factor in most articles.[30] On the contrary, duration of PD was a fairly common bias because DBS patients had necessarily a history of medically treated PD before the loss of efficacy and DBS surgery.[2] Due to mainly small population analysis, missing data or inadequate follow-up or deviation from intervention protocols were rarely a source of bias. The results of the bias analysis are presented in **Table 4**.

Discussion

Our systematic review has served its purpose: the majority of studies reported deterioration of voice and speech parameters after DBS for all areas of stimulation except for pallidal stimulation, the effects of which depend on the area stimulated within the pallidus. The reasons put forward to shed light on this stimulation-induced vocal damage are multiple: effect of age and physiological or disease-related cognitive deterioration with progression of nonmotor disorders, stimulation with diffusion of the electric field to the adjacent areas of the brain involved in the control and production of speech, or damage during the surgical implantation. No proposed mechanism fully explains or can be associated with a specific phenotype of vocal involvement. The issue of decreased quality of life related to vocal impairment, while not systematic or predominant, represents nonetheless a limitation on the complete success of this neurosurgical treatment. The fact remains, however, that DBS has revolutionized the management of PD. Technological and surgical prospects may allow for improvements in these stimulus-induced speech disorders in the near future.

An exhaustive review of the scientific literature published from inception to May 2022 devoted to stimulation-induced voice and speech disorders in PD was carried out. We included 44 publications representing a total of 866 patients. Most studies referred to subthalamic DBS, reflecting current practice and the goal of maximum efficacy with the knowledge and technologies at the time. Methodologically, most studies included a relatively small number of patients. With the exception of the single meta-analysis found,[10] which included 439 patients with DBS, only 2 studies included more than 50 patients with DBS,[16,31] and none included more than 100.

We focused strictly on analysis of publications relating to voice and speech analysis on DBS. Thus, one must keep in mind that DBS is not a treatment for hypokinetic dysarthria induced by PD but the treatment of disability induced by the motor symptoms of this pathology.[8] We must put into perspective the results obtained with regard to vocal parameters and intelligibility with the demonstrated efficacy of DBS for patients' autonomy and quality of life (QoL), otherwise destined to irreversibly and rapidly decrease.

In terms of frequency, dysarthria remains a significant undesirable manifestation of DBS,[32] whether applied to the STN, VIM,[33] or pallidum, with, however, less disturbance if the stimulation is localized to the internal level of the pallidum.[34,35] Likewise, speech disabilities in PD are at the forefront of impairments afflicting patients' QoL, all the more so when treatment affects intelligibility.[36] Data regarding a negative impact of DBS on voice and speech have been subject to conflicting results as well as the important confounding factors of age (patients with DBS are older), the natural history of the disease, and cognitive impairment due to disease or age.[37,38] In 2016, Wyman-Chick[10] provided an answer to the debate by demonstrating a significant alteration in speech fluency in patients with subthalamic DBS (n = 439) compared to 392 patients treated with medications alone.

Fluency is altered with DBS, but this is not the only language parameter studied in the literature that might undergo such a modification. Intelligibility is affected by subthalamic DBS in most series.[39,40] Two studies reported endoscopic evaluation of laryngeal motor activity: the investigators found incomplete glottal closure and compensatory hyperadduction of the ventricular bands responsible for vocal impairment (tightness and murmur in the voice).[16,17] On the other hand, several studies highlight the beneficial nature of DBS on vocal tremor and intensity.[21,31,37] Two studies reported data about improved glottic function (vibration, symmetry, and regularity of the glottic movements and glottic closure) after STN-DBS.[18,19]

From this review of the literature, a consistent effect of DBS on voice and speech is not apparent. A paradox exists between a tendency of some studies to identify a deterioration of the voice subjective evaluation, whereas objective evaluation of the vocal parameters (F0, jitter, shimmer) seems to show a significant improvement after stimulation. Regarding the speech, the results concerning intelligibility and fluency are relatively balanced. A certain polymorphism exists, characterized by multiple patient profiles, aggravated, improved, or neutral, on certain vocal parameters (intelligibility, fluency, intensity, tremor). This clinical variability of voice and

Table 2. Subthalamic Nucleus–Deep Brain Stimulation Effects on Voice and Speech Performance.

Voice/speech quality assessment	Outcomes	Study (first author and year)	Improvement	Deterioration	No significant effect
Voice quality	VHI	Tsuboi 2015[17]; Tanaka 2015[16]		Tsuboi 2015[17]; Tanaka 2015[16]	
	GRBAS, GRBASI, AMSD	Tsuboi 2017[40]; Tsuboi 2015[17]; Tsuboi 2015[31]; Tanaka 2015[16]		Tsuboi 2017[40]; Tsuboi 2015[17]; Tsuboi 2015[31]; Tanaka 2015[16]	
	Acoustic parameters (F0, F2, jitter, shimmer, intensity, harmonic-to-noise ratio)	Behroozmand 2019[57]; Martel-Sauvageau 2017[59]; Van Lancker Sidtis 2010[68]; Lee 2008[69]; D'Alatri 2008[18]; Klostermann 2008[19]; Dromey 2000[70]	Behroozmand 2019[57]; Van Lancker Sidtis 2010[68]; Lee 2008[69]; D'Alatri 2008[18]; Klostermann 2008[19]; Dromey 2000[70]		Martel-Sauvageau 2017[59]
Speech quality	SIT	Chiu 2020[71]; Tanaka 2020[39]; Tanaka 2016[61]; Aström 2010[73]; Klostermann 2008[19]; Törnqvist 2005[20]	Tanaka 2020[39]	Aström 2010[73]; Klostermann 2008[19]; Törnqvist 2005[20]	Chiu 2020[71]; Tanaka 2016[61]
	Fluency (words/min)	Leimbach 2020[56]; Chiu 2020[71]; Romann 2017[60]; Fenoy 2017[45]; Vonberg 2016[38]; Batens 2015[47]; Krugel 2014[63]; Ehlen 2014[46]; Ehlen 2013[49]; Marshall 2012[64]; Silveri 2012[65]; Schulz 2012[66]; Anzak 2011[48]; Xie 2011[67]; Van Lancker Sidtis 2010[68]; Klostermann 2008[19]	Vonberg 2016[38]; Batens 2015[47]; Silveri 2012[65]; Xie 2011[67]; Klostermann 2008[19]	Leimbach 2020[56]; Chiu 2020[71]; Fenoy 2017[45]; Krugel 2014[63]; Ehlen 2014[46]; Ehlen 2013[49]; Marshall 2012[64]; Schulz 2012[66]; Anzak 2011[48]	Romann 2017[60]; Van Lancker Sidtis 2010[68]
	Vowel articulation	Yilmaz 2018[58]; Tanaka 2016[61]; Eklund 2015[62]; Schulz 2012[66]; Klostermann 2008[19]	Yilmaz 2018[58]; Tanaka 2016[61]; Klostermann 2008[19]		Eklund 2015[62]
	Vocalic transition	Chiu 2020[71]; Martel-Sauvageau 2017[59]		Chiu 2020[71]	Martel-Sauvageau 2017[59]
	Verbal production	Chiu 2020[71]; Eklund 2015[62]; Xie 2011[67]; Klostermann 2008[19]	Xie 2011[67]; Klostermann 2008[19]	Chiu 2020[71]	Eklund 2015[62]
	Prolonged phonation	Chiu 2020[71]; Tanaka 2016[61], Xie 2011[67]; Skodda 2011[32]; Klostermann 2008[19]	Xie 2011[67]; Klostermann 2008[19]		Chiu 2020[71]; Tanaka 2016[61]; Skodda 2011[32]
	Repetition	Chiu 2020[71]; Xie 2011[67]; Skodda 2011[32]	Xie 2011[67]	Skodda 2011[32]	Chiu 2020[71]
Laryngeal videostroboscopy	Glottic tremor	D'Alatri 2008[18]; Klostermann 2008[19]	D'Alatri 2008[18]		
	Symmetry of the glottic movements	D'Alatri 2008[18]; Klostermann 2008[19]	D'Alatri 2008[18]; Klostermann 2008[19]		
	Regularity of the glottic movements	D'Alatri 2008[18]; Klostermann 2008[19]	D'Alatri 2008[18]; Klostermann 2008[19]		
	Glottic closure	D'Alatri 2008[18]; Klostermann 2008[19]	D'Alatri 2008[18]; Klostermann 2008[19]		

Abbreviations: AMSD, Assessment of Motor Speech Disorders; GRBAS, Grade, Roughness, Breathiness, Aesthenia, Strain; GRBASI, Grade, Roughness, Breathiness, Aesthenia, Strain, Intensity; SIT, Sentence Intelligibility Test; VHI, Voice Handicap Index.

Table 3. Systematic Review Devoted to the Amelioration or Prevention of Stimulus-Induced Speech Disorders in Parkinson's Disease.

Study (first author and year)	Study design	EL	Cohort	Analysis	Main conclusion
Fabbri 2021[74]	Clinical trial	III	7 M/F: 5/2 Age: 56 y Dd: 11 y	Length: not applicable Comparison: short pulse width (30 μs) vs 60-μs STN-DBS Speech quality outcomes: SIT, speech rate, stuttering dysfluencies Voice quality outcomes: variability, instability Speech material: spontaneous speech/phonetic text	Significant improved speech intelligibly for words and sentences with 30-μs STN-DBS in accordance with patients' perception. Not significant worsened voice variability, instability and stuttering disfluencies. No worsened motor performance with 30-μs STN-DBS.
Piña-Fuentes 2020[27]	Clinical trial	III	13 M/F: 11/2 Age: 46-81 y Dd: 7-24	Length: not applicable Comparison: continue (cDBS) vs adaptative (aDBS) STN-DBS Speech quality outcomes: SIT Voice quality outcomes: 0 Speech material: spontaneous speech	Significantly reduced intelligibility with cDBS but not aDBS
Dayal 2020[25]	Clinical trial	III	16 M/F: 13/3 Age: 66.4 (52-75) y Dd: 11-33 y	Length: not applicable Comparison: short pulse width (30 μs) vs 60-μs STN-DBS Speech quality outcomes: SIT Voice quality outcomes: 0 Speech material: spontaneous speech	No statistically significant difference
Morello 2020[24]	Clinical trial	III	19 M/F: 14/5 Age: 55.3 (31-75) y Dd: 14.6 y	Length: not applicable Comparison: low frequencies (60 Hz) vs high frequencies (130 Hz) STN-DBS Speech quality outcomes: 0 Voice quality outcomes: GRBASI, acoustic parameters (F0, F2, shimmer) Speech material: spontaneous speech	Asthenia and instability improvement, dysarthria aggravation in high frequencies Acoustic parameter stability No significant variation at low frequencies
Fabbri 2019[23]	Comparative	III	Severe dysarthria: 10 M/F: 10/3 Age: 65.3 y Dd: 19 y Mild dysarthria: 10 M/F: 10/3 Age: 63.5 y Dd: 19.9 y	Length: not applicable Comparison: low frequencies (60 Hz) vs high frequencies (130 Hz) STN-DBS Speech quality outcomes: SIT, vowel articulation, fluency Voice quality outcomes: GRBASI, acoustic parameters (F0, F2, shimmer, jitter) Speech material: spontaneous speech/phonetic text/sustained vowels	Significant improvement in joint (diadokokinesis) and SIT with low-frequency DBS
Little 2016[75]	Comparative	III	10 No information	Length: not applicable Comparison: continue (cDBS) vs adaptative (aDBS) STN-DBS. On vs off DBS Speech quality outcomes: SIT Voice quality outcomes: 0 Speech material: phonetic text	Better intelligibility (SIT, $P = .02$) with aDBS than cDBS
Zhang 2016[26]	Retrospective	IV	12 M/F: 7/5 Age: 43-65 y	Length: not applicable Comparison: interleaving stimulation NST-DBS. On vs off DBS Speech quality outcomes: verbal fluency Voice quality outcomes: 0	Dysarthria and less stuttering with interleaving stimulation

(continued)

Table 3. (continued)

Study (first author and year)	Study design	EL	Cohort	Analysis	Main conclusion
				Speech material: spontaneous speech/phonetic text	
Pinto 2014[54]	Cross-sectional	V	7 M/F: 5/2 Age: 56-72 y Dd: 13-29 y	Length: 1 year Comparison: initially and at month 6 with LSVT in 3 groups of 4 patients (4 STN-DBS, 4 LSVT, 4 without DBS or LSVT) Speech quality outcomes: SIT, vowel articulation, prolonged phonation Voice quality outcomes: 0 Speech material: spontaneous speech/phonetic text/sustained vowels	Maximum phonation time, articulatory parameters (diadokokinesis), and intelligibility degradation. Statistical trend
Tripoliti 2011[21]	Clinical trial	IV	Gr DBS: 10 Age: 59.4 y Dd: 13.6 y Gr Med: 10 Age: 63 y Dd: 8.6 y	Length: 6 months Comparison: STN-DBS vs medical treatment. Lee Silverman rehabilitation method evaluation Speech quality outcomes: SIT, verbal fluency Voice quality outcomes: GRBASI Speech material: spontaneous speech/phonetic text	Improvement in intensity in the medical treatment group but not in intelligibility No improvement by LSVT in the DBS group
Spielman 2011[22]	Case control	IV	STN-DBS: 4 M/F: 2/2 Age: 50-84 y Dd: 9-24 y Gr Med: 8 M/F: 5/3 Age: 48-81 y Dd: 2-31 y	Length: 6 months Comparison: initially and at month 6 with LSVT in 3 groups of 4 patients (4 STN-DBS, 4 LSVT, 4 without DBS or LSVT) Speech quality outcomes: vowel articulation Voice quality outcomes: VHI, GRBASI, acoustic measures (sound pressure level) Speech material: spontaneous speech/phonetic text	Improvement of all parameters and maintenance at 6 months for patients treated with LSVT VHI improved significantly in the group with DBS
Aström 2010[73]	Cross-sectional	V	10 M/F: 8/2 Age: 59 y	Length: 6 months Comparison: 4 V (high) and 2 V (low) STN-DBS Speech quality outcomes: prolonged phonation, SIT Voice quality outcomes: 0 Speech material: spontaneous speech/sustained vowels	High-stimulation seems to be consistent with a higher rate of speech impairment, especially when active electrodes are "positioned medial and/or posterior to the center of the subthalamic nucleus"
Törnqvist 2005[20]	Cross-sectional	V	10 M/F: 8/2 Age: 65 y (61-68) Dd: 13 y (11-17)	Length: not applicable Comparison: STN-DBS off vs on; the amplitude was decreased or increased by 25%; the frequency was set to 70, 130, or 185 pps and with a standard setting (2.5 V, 60 μs, 130 pps) Speech quality outcomes: fluency, SIT, overall quality, vowel articulation Voice quality outcomes: 0 Speech material: phonetic text	Intelligibility deteriorated with STN-DBS on in n = 4/10 with standard settings Higher frequencies and amplitudes caused deterioration in intelligibility

Abbreviations: DBS, deep brain stimulation; Dd, disease duration; EL, evidence level; F0, fundamental frequency; Gr DBS, groups: Deep Brain Stimulation; Gr Med, groups: Medical treatment; GRBASI, Grade, Roughness, Breathiness, Aesthenia, Strain, Intensity; LSVT, Lee Silverman voice treatment; SIT, Sentence Intelligibility Test; STN, subthalamic nucleus; VHI, Voice Handicap Index.

Table 4. Bias Analysis.[a]

Reference (first author and year)	Age	Comorbidities	Disease duration	UPDRS-III	Cognitive impairment (MMSE)	DBS duration	Study participants	Deviations from protocol	Missing data
Fabbri 2021[74]	Yes	No	Yes	No	No	Yes	Probably yes	No	No
Leimbach 2020[56]	Yes	No	Yes	No	No	Yes	Probably yes	No	No
Chiu 2020[71]	Yes	No	Yes	No	Yes	Yes	Probably yes	No	No
Tanaka 2020[39]	Yes	Probably yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Behroozmand 2019[57]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Yilmaz 2018[58]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Tsuboi 2017[40]	No	Probably yes	No	Yes	Yes	Yes	Probably yes	Yes	No
Martel-Sauvageau 2017[59]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Romann 2017[60]	Yes	Probably yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Fenoy 2017[45]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Tanaka 2016[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Vonberg 2016[38]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Tsuboi 2015[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Eklund 2015[62]	Yes	Probably yes	Yes	No	No	Yes	Yes	Yes	No
Tsuboi 2015[31]	Yes	Probably yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Batens 2015[47]	No	Probably yes	Yes	No	No	Yes	Probably yes	Yes	No
Tanaka 2015[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Sandström 2015[72]	No	No	Yes	Yes	No	Yes	No	Yes	No
Krugel 2014[63]	Yes	Probably yes	Yes	Probably yes	No	Yes	Yes	Yes	No
Ehlen 2014[46]	No	Probably yes	Yes	Probably yes	No	Yes	Probably yes	Yes	No
Piña-Fuentes 2020[27]	No	Probably yes	No	Yes	No	No	Probably yes	Yes	No
Dayal 2020[25]	Yes	Yes	No	Yes	No	No	Yes	Yes	No
Morello 2020[24]	No	Yes	Yes	Yes	No	Yes	Probably yes	Yes	No
Fabbri 2019[23]	Yes	Probably yes	Yes	Yes	Probably yes	Yes	Yes	Yes	No
Little 2016[75]	No	No	No	Yes	No	Yes	No	Yes	No
Zhang 2016[26]	No	No	No	Yes	No	Yes	No	Yes	No
Pinto 2014[54]	Yes	Probably yes	No	Yes	No	Yes	Probably yes	Yes	No
Dietz 2013[34]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Ehlen 2013[49]	Yes	Probably yes	Yes	Yes	No	Yes	Yes	Yes	No
Marshall 2012[64]	Yes	Probably yes	Yes	Probably yes	Probably yes	Yes	Yes	Yes	No
Silveri 2012[65]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
Schulz 2012[66]	No	No	No	Yes	No	Yes	No	Yes	No
Anzak 2011[48]	Yes	Probably yes	No	Yes	No	Yes	Yes	Yes	No
Xie 2011[67]	Yes	Probably yes	No	Yes	No	Yes	Yes	Yes	No
Tripoliti 2011[21]	Yes	No	No	No	No	No	No	Yes	No
Spielman 2011[22]	No	Yes	No	No	No	Yes	Probably yes	Yes	No
Skodda 2011[32]	Yes	No	Yes	Yes	No	Yes	No	No	No
Aström 2010[73]	Yes	No	No	No	No	Yes	No	No	No
Van Lancker Sidtis 2010[68]	Yes	Probably yes	Yes	Yes	No	Yes	No	No	No
Lee 2008[69]	Yes	Yes	No	Yes	No	Yes	No	No	No
D'Alatri 2008[18]	Yes	Yes	Yes	Yes	No	No	No	No	No
Klostermann 2008[19]	Yes	No	No	Yes	No	No	No	No	No
Törnqvist 2005[20]	Yes	Probably yes	Yes	Yes	No	Yes	No	No	No
Dromey 2000[70]	No	No	No	Yes	No	Yes	No	No	No

Abbreviations: DBS, deep brain stimulation; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale-iii.

[a]According to the bias tool used and the information provided by the authors. Age: yes = ages were provided in each compared group; no = a difference in ages existed between the groups compared. Comorbidities: yes = comorbidities with a high risk of bias on speech or voice performance were taken into account as exclusion criteria; no = no comorbidities figured in exclusion criteria; probably yes = comorbidities were cited but not detailed. Disease duration: yes = disease durations were provided in each compared group; no = a difference in disease durations existed between the groups compared. UPDRS-III: yes = UPDRS-III score was reported in each compared group; no = UPDRS-III score was not reported; probably yes = UPDRS-III was cited in methods but was not reported in the results. MMSE: yes = MMSE score was reported in each compared group; no = MMSE score was not reported; probably yes = MMSE or cognitive assessment was cited in methods but was not reported in the results. DBS duration: yes = DBS durations were provided in each compared group; no = a difference in disease durations existed between the groups compared. Study participants: yes = bias in study participants was prevented

(continued)

with detailed inclusion and exclusion criteria; probably yes = bias in study participants was prevented with detailed inclusion and exclusion criteria but age, comorbidities, or cognitive impairment were not assessed; no = there was a lack in patients' selection criteria to prevent bias. Deviations from intervention protocol: yes = deviation from initial intervention protocol or therapeutic care was not reported; no = deviation from initial intervention protocol or therapeutic care was reported. Missing data or inadequate follow-up: yes = missing data affecting the primary outcomes were reported; no = no missing data affecting the primary outcomes were reported. Analysis conducted using the Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group (McMaster University) and the Agency for Healthcare Research and Quality.

speech features corresponds to the diversity of the disease[41] and its subtypes, from the early to the latter stages, and is to a certain extent affected by an important variation in cognitive impairment.[42,43] This heterogeneity may also correspond to the lack of a specific assessment method for voice and language in PD patients with DBS and to ''a lack of standardization of acoustic measurement methods'' as highlighted by Lechien et al[44] or to the examining physician's experience.[41] Some authors have argued that PD patients with subthalamic DBS have vocal characteristics that might be clustered: patients under stimulation present a persistent worsening of preexisting hypokinetic dysarthria in 1 of 4 cases or develop spastic dysarthria, stammering, vocal tightness, and murmur.[31]

A relationship has been proposed between the activation of the dentato-rubro-thalamic tract and an excessively medial positioning of the left STN stimulation electrode to explain a deterioration in fluency in patients with dominant akinetic rigid disorders[45] or between excessive ventromedial thalamic positioning to explain degradation in verbal fluency in cases of DBS at the level of the VIM.[46] An effect of the laterality of the dopamine deficit of neurons at the level of the STN has also been suggested, with an improvement in verbal fluency only in patients with a predominantly left deficit for bilateral DBS of the STN.[47]

The causes of these vocal and language disturbances remain debated. Diffusion of the stimulation (at the level of the cerebello-thalamic pathways and the internal capsule)[32] and generation of an electrical signal close to the physiological signal necessary for the generation and control of language have been evoked.[48] The overall impairment in verbal and lexical fluency, with no difference between naming of actions or reading after DBS, also suggests the involvement of surgical sequelae linked to the approach rather than the effect of stimulation.[49]

To limit these stimulus-induced disorders, various strategies have been developed. These involve modifications of stimulation parameters or electrode technology. They mainly aim at reducing diffusion of the stimulation to the internal capsule, where fibers involving control and command of language and speech pass through. The intensity of stimulation can be either increased, if the efficacy of DBS is judged to be suboptimal for the akinetic disturbances of the disease, or reduced, if the speech disturbances are judged to proceed from spatial diffusion of the stimulation. The therapeutic margin is narrow.[10] Changes in intensity bear a relationship with changes in frequency. For a decreased frequency, the intensity may be increased. The effects of frequency modulation on stimulation-induced dysarthria are, however, variable.[23,24] Likewise, the pulse duration can be modulated and reduced, with this strategy being based on the following principle: the fast conduction fibers that convey most of the therapeutic effect of DBS respond better to brief stimulations than the internal capsule fibers, with slower conduction resulting in dysarthria.[25]

To spatially limit diffusion of DBS, the stimulation might be directed and focused. A bipolar-type stimulation[50] makes it possible to focus the stimulation by a spatial loop that extends from the negative electrode toward a positive return at the level of the module. Other solutions would be to move the active pad[51] among 4 activatable pads within a stimulation electrode or finally to implant a faceted electrode whose stimulation would be directional.[52] Changing the angle of approach when placing the electrodes[53] and stimulating alternate regions of the STN[54] are other potential approaches to this issue. Nevertheless, the subthalamic site remains the one that has demonstrated the best efficacy for patients' QoL.

A possible limitation are the technological improvement and changes in the surgery and practice accomplished since 1987. Significant changes in the characteristics of implanted devices have taken place since 2014-2015, with the appearance of new neurostimulators allowing for shorter pulse durations[23-25] and also new segmented electrodes allowing for directional stimulation.[51] These modifications are linked to the arrival on the market of new manufacturers who completed the initial offer. These new features quickly changed the practices and granted ways to reduce stimulo-induced speech disorders. This corresponding reduction has been mentioned in various recent articles devoted to new strategies for the adjustment and evaluation of the effects of DBS on speech and voice disorders, and these are included in our review. Other than miniaturization, few major technological differences have been made between 1987 and 2015. However, surgical teams have learned to implant better, and the safety of the procedure, follow-up, and use of these devices have improved (including improved electrode fixation systems with reduced secondary migration). Based on an empirical approach, all results have certainly not been published and may constitute a limitation to our work.

This study's main limitation is the small number of patients included in each study and the heterogeneity in the inclusion and exclusion criteria as the VQ and SQ assessed. Due to the particularly large heterogeneity of the data provided on the SQ and VQ parameters and the means of measurement, whose absence of variability cannot be ensured, no meta-analysis was possible. The statistical analysis was not applicable. The largest number of studies has focused on verbal fluency, a flaw also highlighted by Vos et al.[55] They wrote the only

other systematic review in the field, recently published, with results being in line with ours. However, the systematic review by Vos et al[55] only focused on STN-DBS and language testing while we considered different DBS location, VQ parameters, and more SQ parameters. Further, more articles were included in our review, allowing us to draw a wider panorama on the problematic. To date, the current study represents the largest comprehensive systematic review in the field.

Author Contributions

Robin Baudouin, design, acquisition of paper, analysis and interpretation, drafting, final approval, accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Jérôme R. Lechien**, design, acquisition of paper, analysis and interpretation, drafting, final approval, accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Louise Carpentier**, design, analysis and interpretation, revising the manuscript for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Jean-Marc Gurruchaga**, design, analysis and interpretation, revising the manuscript for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Quentin Lisan**, design, analysis and interpretation, revising the manuscript for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Stéphane Hans**, design, analysis and interpretation, revising the manuscript for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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