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Review Article

The Effect of Deep Brain Stimulation of the Subthalamic Nucleus on Language Function in Parkinson's Disease: A Systematic Review

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Purpose: This systematic review focuses on the effect of bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on language function in Parkinson's disease (PD). It fills an important gap in recent reviews by considering other language tasks in addition to verbal fluency.
Method: We critically and systematically reviewed the literature on studies that investigated the effect of bilateral STN-DBS on language function in PD. All studies included a matched PD control group who were on best medical treatment, with language testing at similar baseline and follow-up intervals as the DBS PD group.
Results: Thirteen identified studies included a form of a verbal fluency task, seven studies included picture naming, and only two studies included more language-oriented tasks. We found that verbal fluency was negatively affected after DBS, whereas picture naming was unaffected. Studies investigating individual change patterns using reliable change indices showed that individual variability is larger for picture naming than for verbal fluency.
Conclusions: Verbal fluency is the most frequently investigated aspect of language function. Our analysis showed a pattern of decline in verbal fluency across multiple studies after STN-DBS, whereas picture naming was unaffected. Data on more language-oriented tests in a large DBS sample and best medical treatment control group are sparse. The investigation of language function in PD after DBS requires sensitive language tests (with and without time pressure) and experimental designs as used in the studies reviewed here. Reliable change index statistics are a promising tool for investigating individual differences in performance after DBS.
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Parkinson's disease (PD) is a neurodegenerative disease characterized by motor symptoms (i.e., bradykinesia with rest tremor and/or rigidity; Berg et al., 2018; Hughes et al., 1992). Beside motor symptoms, patients often suffer from nonmotor symptoms (i.e., autonomic, pain, cognitive, and neuropsychiatric symptoms—some of which are side effects of medication; Schapira et al., 2017; Troster, 2017). Cognitive deficits often occur early in PD and can gradually progress to dementia (Aarsland et al., 2005; Hoogland et al., 2019, 2018; Muslimović et al., 2009, 2005; Weintraub et al., 2018). PD is progressive and cannot be cured. Therefore, interventions are aimed at reducing symptoms, initially by administering medication (i.e., dopamine precursor levodopa or dopamine agonists). If medication no longer controls symptoms sufficiently, more advanced therapies, such as deep brain stimulation (DBS), can be considered for a selective group of patients (Bronstein et al., 2011).

DBS of the subthalamic nucleus (STN) is considered a robust, effective intervention of motor symptoms of PD, such as tremor and rigidity (Deuschl et al., 2006; Fasano et al., 2012; Weaver et al., 2009; Williams et al., 2010). However, the effects of DBS on cognitive outcome have been subject to discussion, especially with respect to verbal fluency (Mehanna et al., 2017; Rossi et al., 2018; Voon et al., 2006; Witt et al., 2008).

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Cognitive function is measured by using neuropsychological tests covering important cognitive domains (e.g., memory, executive functioning, attention and concentration, psychomotor speed, visuoperceptual spatial ability, language; see Marras et al., 2014). Such a test battery is often a standard part of the preselection process for the choice of DBS treatment, as dementia (see Dubois et al., 2007; Emre et al., 2007, for criteria of PD dementia) is an exclusion criterion (see Kubu et al., 2018; Massano & Garrett, 2012; Troster, 2017, for an in-depth discussion).

At present, there are several reviews and meta-analyses available that have investigated differences in cognitive performance pre– and post–DBS surgery (Castrioto et al., 2014; Combs et al., 2015; Fasano et al., 2012; Halpern et al., 2009; Massano & Garrett, 2012; Mehanna et al., 2017; Parsons et al., 2006; Temel et al., 2006; Xie et al., 2016). However, all reviews have identified the problem that there are hardly any randomized controlled studies available. Also, the published studies vary in experimental setup and statistical analyses; patient selection; surgical procedures used; the location and intensity of electrode stimulation; and differences in outcome measures, medication prescriptions, and dosages. Furthermore, from a neuropsychological perspective, studies differ in the way they defined and assessed independent cognitive domains. This is indeed not a straightforward task, as many cognitive tests tap into more than one single cognitive function or domain (see Massano & Garrett, 2012). Nevertheless, despite all these shortcomings, these reviews generally converge on the finding that "verbal fluency" is the task showing the most consistent and largest decrement postsurgery, whereas other cognitive functions do not show this systematic decline (Castrioto et al., 2014; Combs et al., 2015; Fasano et al., 2012; Halpern et al., 2009; Massano & Garrett, 2012; Mehanna et al., 2017; Parsons et al., 2006; Temel et al., 2006; Xie et al., 2016).

Verbal fluency is measured by asking people to produce, within a certain time period, as many words as possible from a certain semantic category (e.g., animals; referred to as semantic or category fluency) or beginning with a certain letter (e.g., "K"; referred to as phonemic or letter fluency). For many languages, there are normed and standardized fluency tests available, such as the widely used Controlled Oral Word Association Test in English (Lezak et al., 2012; Patterson, 2011). Such fluency tests are sometimes categorized under the cognitive domain "language" and sometimes under that of "executive function," as fluency involves multiple cognitive processes (e.g., lexical search, memory retrieval, executive function). Regarding the brain areas involved in this task, neuropsychological investigations implicate both prefrontal and temporal lobe areas, with prefrontal areas being more important in phonemic fluency and the temporal lobe areas in semantic fluency (Baldo et al., 2006).

A recently published meta-analysis focused on the changes in verbal fluency after DBS surgery in PD by selecting only those studies that compared a DBS PD group with a nonsurgical PD group treated by medication only (Wyman-Chick, 2016). This critical selection ensured that deterioration in verbal fluency could not be ascribed to disease progression itself. The meta-analysis yielded a final selection of 10 studies reported between 2000 and 2014 with a nonsurgical PD control group and a bilateral STN-DBS group. It showed that verbal fluency was more affected in the STN-DBS group than in the nonsurgical group, with a medium effect size for phonemic fluency ($d = -0.47$) and a small effect size ($d = -0.31$) for semantic fluency.

The reliability of the reports for a decline in verbal fluency and the suggested underlying mechanisms have been discussed in a review by Højlund et al. (2017). Their overall conclusion was that there is indeed reliable evidence for a worsening of both phonemic and semantic verbal fluency after STN-DBS, but there is no clear explanation of the underlying causes. They systematically reviewed hypotheses concerning disease progression, reduced dopaminergic medication levels, electrode position, and stimulation parameters or surgery effects, but their results were inconclusive.

The present systematic review aims to fill a gap in previously published reviews, namely, the absence of reports on language tasks other than verbal fluency. The literature clearly indicates that verbal fluency is the cognitive task that worsens most after STN-DBS. However, it is currently unknown what the underlying mechanism is that causes this decline. The task itself taps into several different cognitive processes, both executive and linguistic.

To explore a potential underlying mechanism, some studies compared the worsening in verbal fluency after STN-DBS with "other" executive function tasks or with reductions in speed of processing (Foley et al., 2017; Marshall et al., 2012). Results of these individual studies, however, were inconclusive. Furthermore, there has been no review that compared verbal fluency with other language tasks, leaving a potential linguistic explanation uninvestigated.

To fill this gap, we performed a literature search on studies including some form of language task as an outcome measure of DBS treatment in PD. Whereas previous reviews included search terms as "cognition," "executive function," or specifically "verbal fluency" (Castrioto et al., 2014; Combs et al., 2015; Fasano et al., 2012; Halpern et al., 2009; Højlund et al., 2017; Massano & Garrett, 2012; Mehanna et al., 2017; Parsons et al., 2006; Temel et al., 2006; Wyman-Chick, 2016; Xie et al., 2016), we included the broader term "language." In this way, we aimed to identify more language-oriented studies other than the language tasks in neuropsychological test batteries included in earlier reviews. Moreover, following the recommendations from recent reviews (Højlund et al., 2017; Wyman-Chick, 2016), we only included studies that compared an STN-DBS group with a matched control group of patients with PD on best medical treatment (BMT) and without surgery. In this way, we controlled for the fact that decline in language after STN surgery could be ascribed to disease progression itself. Thus, the current review focuses on the effect of bilateral STN-DBS in PD on language function by investigating verbal fluency and other potential language tasks that have not yet been reviewed systematically.

Method

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for performing and reporting a systematic review (Moher et al., 2009; see Supplemental Material S1). A literature search was conducted using the Web of Science Core Collection in February 2018, which was updated in July 2020 by performing an additional search through PubMed. Key words used were "deep brain stimulation" AND "Parkinson" AND "language," yielding 76 hits. These articles were independently analyzed by a neuropsychologist (S. V.) and a linguist (V. P.) to check whether they fulfilled the selection criteria (see below and Figure 1). The reference lists of the selected articles and of the key reviews mentioned above were further hand-searched for potentially relevant articles that address language following STN-DBS.

We used strict selection criteria to decrease variability among studies as much as possible. All patients involved in the studies suffered from the idiopathic form of PD. The surgery group underwent bilateral DBS of the STN, and the control PD group had to be on BMT without surgery. Both groups performed the language tasks twice at similar time intervals; for the DBS group, this was between 1 week and less than 3 months before surgery and at least 3 months after surgery. If the language task was part of an extensive neuropsychological test battery, the language part was analyzed separately if those data were reported. We only included studies with clearly described methods and results that were not reported across multiple publications.

In summary, studies were included if they fulfilled the following criteria: (a) Patients suffered from idiopathic PD; (b) The surgery PD group had bilateral STN-DBS, and the nonsurgical PD group was treated with medication only (BMT group); (c) The outcome measure was a language task; (d) This language task was administered with the same time intervals for the DBS and BMT groups; (e) At each time point, the language task was measured under optimal medical conditions for each group, that is, with optimal medication dosages and stimulation dosages; (f) For the DBS group, the language assessment was administered before surgery and at least 3 months after surgery; (g) Methods and results were clearly described; (h) Results were not described across multiple publications.

The following variables were extracted: the number of patients with PD in the DBS and BMT groups, age and education level, disease duration, motoric evaluation off medication, the outcome of general cognitive tests, dopaminergic therapy, and exclusion criteria for both the DBS and BMT groups. With respect to the language tests, we extracted whether the language test was part of a neuropsychological test battery, the time points of measurement before and after surgery, details of the language tests, the language of test administration, and any other remarks on results and statistical procedure. The results of the language tests were extracted as reported by the authors. Reliability in identifying studies was maintained by having the two authors perform the literature search, systematically go through the database, and check the reference

Figure 1. Selection process of literature. DBS = deep brain stimulation; PD = Parkinson's disease; STN = subthalamic nucleus.

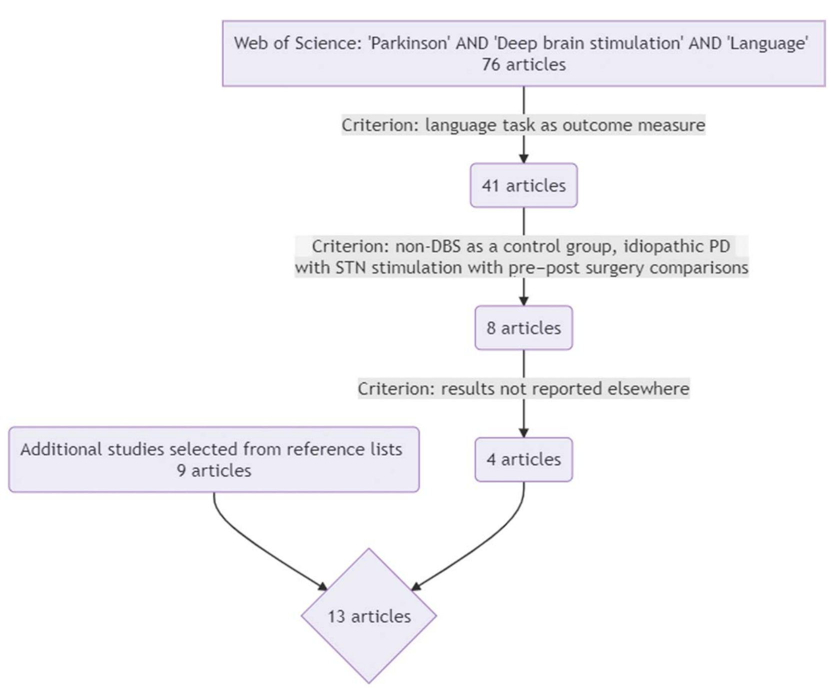


Table 1. Summary of the demographic and clinical data of the deep brain stimulation (DBS) and best medical treatment (BMT) groups of patients with Parkinson's disease (PD) represented in the 13 selected studies at baseline.

Study	No. of patients with PD in the DBS and BMT groups	Age in years, *M* (*SD*)	Education level in years	Disease duration in years, *M* (*SD*)	Motoric evaluation UPDRS III off medication	Motoric evaluation Hoehn & Yahr off medication	Outcome general cognitive test	Dopaminergic therapy mg/day (*SD*)	Exclusion criteria for both groups	Additional remarks
Gironell et al. (2003)	8 DBS	56.6 (4.8)	9.4 (5.6)	12.5 (4.8)	59.9 (15.5)	4.3 (0.6)	28.0 (0.9)	1,020.0 (490.2)	MMSE < 25 Age > 70 Major depression	Another research group included 8 PD unilateral pallidotomy.
	8 BMT	55.8 (7.2)	8.3 (2.2)	11.7 (4.7)	55.2 (8.7)	4.2 (0.7)	28.2 (1.4) MMSE	995.3 (340.3)	Marked cerebral atrophy on MRI	The BMT group were patients who declined DBS surgery.
Moretti et al. (2003)	9 DBS 9 BMT	68.7 (7.9) 69.5 (7.1)	8.9 (2.3) 8.7 (1.5)	11.3 (5.7) NR	61.7 (NR) NR	4.01 (NR) NR	NR NR	1,432 (NR) NR	Depression	
Whelan et al. (2003)	5 DBS 16 BMT	63.2 (4.8) 64.4 (8.4)	11.4 (3.0) 12.0 (4.1)	10.8 (4.1) 7.3 (5.5)	NR NR	3.2 (1.3) 2.3 (0.8)	NR NR	NR NR	Outside normal range on DRS Other neurological or psychiatric diseases Preliminary language deficits Patients with more than mild dysarthria	A third group consisted of 16 HC, with ages of 61.9 years (9.0) and education level of 12.6 (4.5).
Morrison et al. (2004)	17 DBS	59.9 (7.7)	15.4 (2.6)	10.8 (3.4)	NR	3.2 (0.8)	137.8 (5.6) DRS 110.3 (8.2) NART-R	NR	Outside normal range on DRS and on the NART-R	Two patients in the DBS group already had right-sided pallidotomy.
	11 BMT	62.7 (11.5)	13.8 (2.6)	10.0 (3.0)	NR	3.3 (0.6)	136.8 (4.2) DRS 103.5 (10.0) NART-R			
Smeding et al. (2006)	99 DBS	57.9 (8.1)	11.0 (2.9)	13.7 (6.1)	43.6 (12.5)	3.7 (0.9)	102.6 (13.4) DART-IQ 136.1 (5.4) DRS	899.3 (498.0)	Severe brain atrophy on CT or MRI scans Hoehn & Yahr Stage 4 or 5 in the best "on" phase	
	36 BMT	63.0 (9.1)	12.4 (3.0)	10.4 (4.6)	NR	NR	106.3 (10.3) DART-IQ 137.0 (5.4) DRS	629.6 (304.9)	Predominantly unilateral symptoms without severe response fluctuations DRS < 120 Depression or psychosis at inclusion	
Witt et al. (2008)	60 DBS 63 BMT	60.2 (7.9) 59.4 (7.5)	NR	13.8 (6.3) 14.0 (6.1)	47.9 (13.1) 47.3 (11.9)	3.62 (0.85) 3.77 (0.86)	139.6 (3.8) 140.0 (3.5) DRS	1,203 (535) 1,142 (463)	DRS < 131 (dementia) Psychiatric illness	Randomized multicenter study

(*table continues*)

Table 1. *(Continued).*

Study	No. of patients with PD in the DBS and BMT groups	Age in years, *M* (*SD*)	Education level in years	Disease duration in years, *M* (*SD*)	Motoric evaluation UPDRS III off medication	Motoric evaluation Hoehn & Yahr off medication	Outcome general cognitive test	Dopaminergic therapy mg/day (*SD*)	Exclusion criteria for both groups	Additional remarks
York et al. (2008)	23 DBS	59.5 (11.8)	14.4 (2.6)	12.0 (5.5)	49.3 (11.3)	2.28 (0.42)	28.1 (3.0) MMSE 135.3 (9.0) DRS	1,009.8 (445.2)	MMSE < 24 Psychiatric complications that might interfere with compliance	The DBS group had a significantly lower education, younger age, longer duration of illness, and higher dopaminergic medication than the BMT group before surgery (used as covariates in statistical analyses).
	28 BMT	66.7 (8.7)	16.3 (1.3)	4.7 (4.4)	NR	2.13 (0.58)	28.9 (1.1) MMSE 138.7 (5.0) DRS	358.9 (287.0)	Hoehn & Yahr “on” score of 5 Medical contraindications to surgery Intracranial abnormalities on MRI	
Castelli et al. (2010)	27 DBS 31 BMT	60.6 (6.7) 60.2 (6.6)	8.0 (4.1) 9.0 (4.1)	15.3 (5.1) 15.6 (5.2)	55.0 (11.3) 49.6 (11.9)	NR NR	NR NR	1,046.1 (436.4) 1,071.3 (370.3)	Dementia, depression, or psychiatric disorder Marked atrophy on brain scans Age > 70	
Zangaglia et al. (2009)	32 DBS 33 BMT	58.8 (7.7) 62.5 (6.8)	7.3 (3.2) 7.6 (3.6)	11.8 (5.1) 10.0 (4.9)	40.1 (15.5) 35.0 (12.2)	3.2 (0.7) 3.0 (0.7)	28.2 (2.0) 28.2 (1.7) MMSE	932.9 (409.9) 1,043.5 (304.9)	Dementia (MMSE ≤ 24) Psychiatric disease	Of the 33 BMT patients, 7 chose apomorphine therapy and 26 had modification of their routine oral therapy instead of DBS.
Rinehardt et al. (2010)	20 DBS 20 BMT	66.7 (9.4) 69.3 (6.5)	13.4 (2.3) 12.1 (2.8)	9.4 (5.1) 7.5 (5.9)	30.5 (17.4) 23.8 (14.6)	3.2 (0.5) 2.6 (0.5)	27.8 (2.3) 26.8 (2.9) MMSE	NR NR	Dementia Other neurological diseases History of psychiatric disease	The DBS PD group had significantly worse UPDRS scores than the BMT PD group.
Sáez-Zea et al. (2012)	9 DBS	54 (14)	3 < primary 3 primary 3 secondary	12 (2)	43 (15)	3 (*N* = 2) > 3 (*N* = 7)	NR	1,529 (640)	Presence of another disease that has a poor medium-term survival	The BMT group voluntarily refused DBS.
	12 BMT	62 (10)	7 < primary 3 primary 2 secondary	15 (6)	49 (11)	3 (*N* = 5) > 3 (*N* = 7)	NR	1,359 (340)	Marked functional disability or postural instability in “on” state Cognitive impairment Severe active psychiatric disorder Depression Brain atrophy or anomalies	

(*table continues*)

Table 1. *(Continued).*

Study	No. of patients with PD in the DBS and BMT groups	Age in years, *M* (*SD*)	Education level in years	Disease duration in years, *M* (*SD*)	Motoric evaluation UPDRS III off medication	Motoric evaluation Hoehn & Yahr off medication	Outcome general cognitive test	Dopaminergic therapy mg/day (*SD*)	Exclusion criteria for both groups	Additional remarks
Rothlind et al. (2015)	84 DBS 116 BMT	61.3 (8.5) 62.3 (8.9)	15.2 (3.3) 14.8 (3.0)	11.0 (5.0) 12.8 (5.5)	42.8 (16.7) 43.1 (11.2)	3.4 (0.9) 3.3 (0.9)	NR NR	1,291.5 (549.8) 1,290.1 (550.2)	Atypical syndromes Dementia (MMSE < 25) Previous surgery for PD Active alcohol and drug abuse Pregnancy	Patients were randomized to either DBS or BMT.
Demeter et al. (2017)	10 DBS 10 BMT on waiting list	54.8 (5.9) 64.2 (10)	13.5 (2.4) 13.2 (3.5)	8.6 (2.5) 8.1 (3.8)	48.2 (10.4) 50 (6.5)	3.6 (0.5) 3.8 (0.4)	28.5 (1.4) 28.4 (1.4) MMSE	606.7 (250.2) 821.1 (389.6)	Dementia (MMSE ≤ 24) Depression BDI > 19 Other psychiatric or neurological disease Alcohol abuse/drug dependence	The patient group on waiting list was significantly older than the DBS group.

Note. All patients suffered from idiopathic form of Parkinson's disease. UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NR = not reported; DRS = Dementia Rating Scale; HC = healthy controls; NART-R = National Adult Reading Test–Revised; DART = Dutch Adult Reading Test; CT = computed tomography; BDI = Beck Depression Inventory.

lists of a relevant article for identifying studies that may have been overlooked. The inclusion criteria were strict, and potential disagreements on the selection process were resolved by discussion resulting in unity. We did not use any method to assess the risk of bias of individual studies (but see Table 1 for details on exclusion criteria of patients per study).

Results

Excluded Studies

Of the original 76 articles identified by searching the database, most articles (35) were rejected because they did not fulfill the criterion of having a language task as outcome measure (see Figure 1). The search term "language" was intentionally broad, as we did not want to overlook potentially relevant articles, but also resulted in irrelevant hits, not least because it triggered statements in the text about the language the article was written in. Furthermore, the search strategy triggered speech-related investigations that were beyond the scope of this review. We refer the reader to Alomar et al. (2017) for a meta-analysis on speech after DBS PD related to dysarthria, dysphasia, and hypophonia; to Aldridge et al. (2016) for a systematic review on speech aspects such as intelligibility, acoustic measures, self-perception of speech, articulation accuracy and/or rate, oromotor, and laryngeal articulation after STN-DBS; and to Wertheimer et al. (2014) for the patient's perspective of speech changes after DBS. The language performance–related items of the Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987; Goetz et al., 2008) were considered insufficiently sensitive to measure change and were not taken into account, as these only consisted of some general questions about speech and forgetfulness. Even when studies did include a language task as a dependent measure, the critical criteria of having a PD BMT control group, bilateral STN target location, and pre–post surgery comparisons were not fulfilled in another 33 studies from the database selection. Many of these excluded studies reported different types of language tasks other than verbal fluency, but their aim was to investigate the role of the STN in normal language processing by comparing on–off stimulation conditions instead of pre–post surgery conditions (e.g., Batens et al., 2014, 2015; Bridges et al., 2013; Castner et al., 2008, 2007; Krugel et al., 2014; Phillips et al., 2012; Silveri et al., 2012; Tomasino et al., 2014; Tremblay et al., 2015; Vonberg et al., 2016; Whelan et al., 2005). Finally, we excluded four studies from the database selection and one study from searching the reference list because they were cohorts of data already reported elsewhere with different study interests or were (longitudinal) follow-up studies: Zangaglia et al. (2012) is a follow-up study of Zangaglia et al. (2009), Smeding et al. (2011) is a follow-up study of Smeding et al. (2006), Marshall et al. (2012) and Williams et al. (2011) are follow-up studies of York et al. (2008), and Daniels et al. (2010) is a follow-up study of Witt et al. (2008).

Results Concerning Patient Selection and Experimental Details of the Included Studies

In total, 13 studies fulfilled the selection criteria, four studies from the initial search through the database and nine studies by extensive hand searching through reference lists and reviews. Tables 1 and 2 present the (experimental) details of each study. The final selection of 13 studies shows that—even with strict selection criteria—the studies differ largely on demographic and clinical data of the DBS and BMT PD groups, as listed in more detail in Table 1 (Castelli et al., 2010; Demeter et al., 2017; Gironell et al., 2003; Moretti et al., 2003; Morrison et al., 2004; Rinehardt et al., 2010; Rothlind et al., 2015; Sáez-Zea et al., 2012; Smeding et al., 2006; Whelan et al., 2003; Witt et al., 2008; York et al., 2008; Zangaglia et al., 2009).

Five out of 13 selected studies included less than 10 patients in one or both study arms. Only three studies included more than 60 STN-DBS patients (Rothlind et al., 2015; Smeding et al., 2006; Witt et al., 2008), with two having a randomized controlled trial design (Rothlind et al., 2015; Witt et al., 2008). At baseline, all 13 selected studies matched the two experimental groups as much as possible in terms of age, education level in years, and disease duration, followed by characteristics such as motoric evaluation, dopaminergic therapy, and outcome of a general cognitive test. Four out of the 13 studies did not report statistical results of this matching process (Moretti et al., 2003; Smeding et al., 2006; Whelan et al., 2003; Witt et al., 2008). General exclusion criteria were depression, dementia, or other neurological or psychiatric diseases. One study explicitly reported preselection on the absence of speech and language disorder (Whelan et al., 2003).

All 13 selected studies tested patients in their most optimal condition, that is, with optimal medication and with stimulators on optimal settings. Morrison et al. (2004) included two more experimental conditions, namely, testing of language performance with the stimulation off and off medication (not reviewed here).

Statistical analyses showed considerable heterogeneity. Seven studies investigated change scores (i.e., the postoperative score minus the preoperative score) within each group and performed analyses on differences in change scores (Castelli et al., 2010; Demeter et al., 2017; Rothlind et al., 2015; Sáez-Zea et al., 2012; Smeding et al., 2006; Witt et al., 2008; Zangaglia et al., 2009). One study transformed raw scores into standardized scores (Morrison et al., 2004). Five studies used the approach in which individual scores are interpreted according to normative scores of a reference control group (reliable change indices [RCIs]; Rinehardt et al., 2010; Rothlind et al., 2015; Whelan et al., 2003; Witt et al., 2008; York et al., 2008). With this approach, the clinical relevance of the individual's score is more readily interpretable in terms of decline, improvement, or stable condition. One study reported only on decline scores (Rothlind et al., 2015), whereas others reported on all three potential change conditions (Rinehardt et al., 2010; Whelan et al., 2003; Witt et al., 2008; York et al., 2008). Finally, a single-

Table 2. Details of language test performances of the 13 included studies.

Study	Language test as part of a neuropsychological test battery	Time point of measurement before surgery	Time point of measurement after surgery	Specifications of language tests	Language used in tests	Results for language tests	Additional remarks on results and statistical procedure
Gironell et al. (2003)	Yes	1 month	6 months	Two types of fluency tests: 1. Semantic fluency (animals, 1 min) 2. Phonemic fluency (letters, 1 min)	NR	Worsening of semantic fluency for DBS but not for BMT No differences in phonemic fluency	
Moretti et al. (2003)	Yes	NR	1, 6, and 12 months	Three types of fluency tests: 1. Semantic fluency 2. Phonemic fluency (1 and 2 tested as alternating) 3. Syllabic phonemic fluency test (measuring nr of words produced and intrusion errors) From Bilingual Aphasia Test Part B: Syntactic and Morphological tests (errors)	Italian	Worsening of all three types of fluency at the three time points after surgery for DBS as compared to BMT DBS group made more intrusion mistakes at 1 month postsurgery but recovered after 12 months After 12 months DBS: improvement in syntactic complexity processing (fewer mistakes) than in BMT; no differences in mistakes for morphology at any time point	Between-groups analyses were performed per time point, and a within-group analysis was performed for the DBS group in which pre and post differences were assessed.
Whelan et al. (2003)	No	Up to 1 month	3 months	Three extensive language assessment batteries, including (see original article for more details): 1. Neurosensory Center Comprehensive Examination for Aphasia and Boston Naming Test (BNT) 2. Test of Language Competence–Expanded Edition, the Word Test–Revised (TWR), and animal and tool semantic fluency 3. Lexical decision task (LDT) with words and pseudowords	English	DBS group: NS for fluency and BNT Greater proportion of reliable improvement in DBS vs. BMT on TWR in multiple definitions subtest Greater proportion of reliable decline in DBS vs. BMT in accurately identifying real words with rich meaning in LDT	Reliable change index scores were calculated per PD group and compared to a healthy control group. Proportions of reliable change were then compared between the DBS and BMT groups.

(*table continues*)

Table 2. *(Continued).*

Study	Language test as part of a neuropsychological test battery	Time point of measurement before surgery	Time point of measurement after surgery	Specifications of language tests	Language used in tests	Results for language tests	Additional remarks on results and statistical procedure
Morrison et al. (2004)	Yes	Before: NR	Average of 13 weeks BMT: ~9 weeks between two tests After surgery: two test moments with 10 days in between (with 7 days range) for on–off condition	Three types of fluency tests: 1. Semantic fluency (occupation, food, kitchen items) 2. Phonemic fluency (letter) 3. Alternating verbal fluency: used for executive functioning composite score BNT (short form) BNT and semantic and phonemic fluency are combined into one language composite score	English	Worsening in language based on composite score (BNT and fluency tests) for the DBS group No differences in language composite score in BMT group over time	The design had a pre- and postsurgery measurement (both "on" and "off" stimulation or medication measurements). Here, only "on" is reported. Five DBS patients were off PD medication during all test moments; the remaining patients declined the "off" condition because of physical discomfort. In contrast, all BMT patients were off medication.
Smeding et al. (2006)	Yes	< 3 months	> 6 months	Three types of fluency tests: 1. Semantic fluency (2 min) 2. Phonemic fluency (3 min) 3. Alternating verbal fluency (4 min) BNT	Dutch	Worsening pre vs. post on all three fluency tasks compared to BMT group No significant changes for BNT	Change scores were calculated as the score at follow-up minus the score at baseline, and then change scores were tested between PD-DBS compared to PD-BMT.
Witt et al. (2008)	Yes	< 6 weeks	6 months	Two types of fluency tests: 1. Semantic fluency (male/female names, plants, and animals) 1 min, 2 runs 2. Phonemic fluency (letters) 1 min, 2 runs	German	Worsening of semantic fluency (Cohen's $d = -0.4$) and phonemic fluency (Cohen's $d = -0.5$) for DBS group	Randomized multicenter study Statistical analyses were done on change scores: defined as more than 1 *SD* outside the mean of the control group without DBS.
York et al. (2008)	Yes	1.5 months	6 months	Two types of fluency tests: 1. Semantic fluency (animals) 2. Phonemic fluency (letter) BNT	English	Marginally significant worsening of phonemic fluency for DBS group as compared to BMT No differences for BNT or for semantic fluency Based on RCI on individual level: 26% of patients worsened in phonemic fluency vs. 4% of the BMT patients	Individual change scores were based on RCI statistics.

(*table continues*)

Table 2. *(Continued).*

Study	Language test as part of a neuropsychological test battery	Time point of measurement before surgery	Time point of measurement after surgery	Specifications of language tests	Language used in tests	Results for language tests	Additional remarks on results and statistical procedure
Castelli et al. (2010)	Yes	2 weeks	1 year	Two types of fluency tests: 1. Semantic fluency 2. Phonemic fluency	Italian	Worsening of phonemic fluency after 1 year for DBS group as compared to BMT group No difference for semantic fluency	Statistical analyses were based on change scores (measurement postsurgery minus measurement presurgery) and then analyzed between groups.
Zangaglia et al. (2009)	Yes	1–2 months	3 years	Phonemic fluency (letter)	Italian	Trend for worsening of phonemic fluency for DBS group over time as compared to BMT group	More time points of measurement were additionally reported at 1, 6, 12, and 24 months after DBS surgery for the DBS group.
Rinehardt et al. (2010)	Yes	1 month	3–4 months Retest interval of 5 months in BMT	Picture naming Semantic fluency (fruits and vegetables, 1 min) Both subtests were taken from the Repeatable Battery of Neuropsychological Status (RBANS)	English	No differences on group level between groups Differences in RCI based on regression analysis In DBS group: 15% worsening in semantic fluency vs. 0% in BMT group In DBS group: 40% worsening in picture naming vs. 10% in BMT group	Standardized regression-based approach RBANS index “language” consists of picture naming and semantic fluency.
Sáez-Zea et al. (2012)	Yes	1–2 weeks	After: 6 months	Two types of fluency tests: 1. Semantic fluency (animals), 1 min 2. Phonemic fluency (letters), 1 min BNT	Spanish	Decline in verbal fluency in both groups over time Marginally stronger deterioration of phonemic fluency for the DBS group than the BMT group No differences for BNT	
Rothlind et al. (2015)	Yes	NR	> 6 months	Two types of semantic fluency tests 1. Semantic fluency (animals and grocery) 2. Phonemic fluency (letters) BNT	English	Decline in semantic fluency, phonemic fluency after DBS as compared to BMT (there was no difference in DBS target location; data were pooled over STN and GPi)	Patients were randomized to either DBS or BMT.
Demeter et al. (2017)	Yes	NR For both groups: time difference between two assessment points = 4–6 months	NR	Two types of semantic fluency tests: 1. Semantic fluency 2. Phonemic fluency	Hungarian	Decline in semantic fluency after DBS compared to control group No effect for phonemic fluency	Individual change scores were measured: post–pre. Then, statistical analyses were performed on these change scores per group.

Note. Results described are significant in the original articles, unless otherwise stated. All patients suffered from idiopathic form of PD. Presurgery time points and postsurgery time points count for the DBS PD group. The BMT group had similar time intervals unless otherwise stated. NR = not reported; DBS = deep brain stimulation; BMT = best medical treatment; NS = not significant; PD = Parkinson’s disease; RCI = reliable change index; STN = subthalamic nucleus; GPi = globus pallidus internus.

case analysis by means of multivariate normative comparisons has been used (Castelli et al., 2010).

Specification of Language Tests and Language Performance Outcome

Eleven out of the 13 selected studies investigated language performance by extracting the language test(s) out of a broader neuropsychological test battery. All 13 studies included some form of fluency task, and in addition, there were seven studies with picture naming and two studies with other language tasks. Figure 2 presents for each type of language task the number of studies that reported no significant change, significant worsening, marginally significant worsening, or improvement after DBS (see Table 2 for details).

Verbal Fluency

Twelve studies included a semantic fluency task, and 11 included a phonemic fluency task. Although all articles refer to "semantic fluency" and "phonological, phonemic or letter fluency," there are differences in the way the fluency test is administered. Most studies used a fluency test in which the production of words in 1 min was measured, but some used up to 3 min (Smeding et al., 2006). Moreover, the semantic categories varied between male/female names, plants, animals, occupation, food, and kitchen items, and the letters differed across studies. The tests were performed in six different languages (English, Italian, Spanish, German, Dutch, and Hungarian). Two studies focused on alternated fluency as well, by systematically alternating the phonemic and semantic fluency subtasks, which has a larger demand on executive functioning (Morrison et al., 2004; Smeding et al., 2006). One study (Moretti et al., 2003) included an alternating syllabic phonological fluency test in which patients were trained to produce as many words beginning with a syllable in 1 min. It measured not only the total number of produced words but also the number of intrusion mistakes (e.g., the requested syllable was "tra," but an intrusion mistake occurred when words beginning with "ter," "ta," or "tu" were produced).

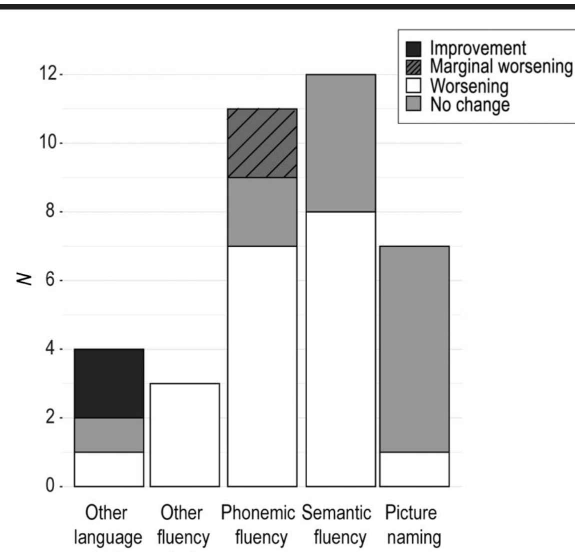
Table 2 shows that, despite differences in task administration, language used, and type of fluency test, in general, there is a decline in fluency in the STN-DBS group as compared to the BMT group. Figure 2 shows that, with all fluency measures combined, there was a significant worsening in 69% of the studies, a trend for worsening in 8%, no change in 23%, and no study reporting an improvement of verbal fluency for the STN-DBS group as compared to the BMT group.

With respect to the use of RCI statistics, two studies found an overall significant difference between the STN-DBS and BMT groups (Rothlind et al., 2015; Witt et al., 2008), whereas three other studies did not find such significant differences at the group level (Rinehardt et al., 2010; Whelan et al., 2003; York et al., 2008). Rinehardt et al. (2010) then explored within groups the individual differences in RCI and found that, for semantic fluency, 15% of the STN-DBS patients declined and 0% improved, whereas in the BMT group, none of the patients declined on semantic fluency and 5% improved. York et al. (2008) found that 26% of the patients who underwent DBS demonstrated a significant, reliable decline in phonemic fluency compared with only 4% of the BMT patients. For semantic fluency, these percentages were 40% versus 30.4%, respectively.

Picture Naming

Picture naming has not previously been reviewed in the DBS literature as a separate language task. The Boston Naming Test (BNT; Lezak et al., 2012), in particular, is

Figure 2. Number of studies showing improvement, worsening, or no change after deep brain stimulation surgery for the different language tasks. Note that the summary provided here is oversimplified, and the reader is referred to Table 2 for details.



frequently included as a standard picture-naming test in the neuropsychological test battery referring to the cognitive domain "language." It is used to test confrontation naming by showing pictures of objects that have to be named. The frequency of the pictures' names varies, and importantly, there are no strict time limits. The scoring is based on errors in naming or failures to name. From the final 13 selected studies shown in Table 1, six studies included the BNT, and one included another picture-naming test (Rinehardt et al., 2010). In the latter study, picture naming was part of the language domain from a broader neuropsychological test battery. As with the BNT, subjects were requested to name line drawings without time pressure. Interestingly, none of the studies found any differences before and after DBS on test performance as compared to the BMT control group at the group level (see also Figure 2). Thus, picture-naming (without strong time limits) performance does not seem affected after DBS compared to BMT at the group level, but more studies and a meta-analysis are needed to confirm this.

Although there were no significant differences in RCI patterns between the STN-DBS and BMT groups, three studies explored the results at the individual patient level (Rinehardt et al., 2010; Whelan et al., 2003; York et al., 2008). Whelan et al. (2003), with only five STN-DBS patients, found that two STN-DBS patients improved, two STN-DBS patients declined, and one STN-DBS patient did not show any reliable change after DBS surgery. None of the BMT patients (n = 16) declined on the BNT, whereas 19% improved. Also, Rinehardt et al. (2010) found no significant decline at the group level. However, on an individual level, they found that 40% of the patients declined in picture naming and 5% improved after STN-DBS surgery, whereas 10% of the BMT patients declined and 5% improved. Finally, York et al. (2008) found that, after DBS, 23% of the patients declined in picture naming whereas 14% improved, and 4% of the patients declined and 7% improved in the BMT control group. Thus, RCI analyses provide some indication that picture-naming abilities may decline after STN-DBS for a subset of individuals relative to a BMT control group.

Other Language Tests

Moretti et al. (2003) investigated language function by including three tests of verbal fluency (semantic, phonological, and syllabic) and two subtests of the (Italian) Bilingual Aphasia Test (BAT; Part B), measuring syntactic comprehension and morphological processing. In the syntactic comprehension section of the BAT, the participant is instructed to touch the picture or part of a picture that corresponds to a given sentence within a certain time limit (5 s). In this section, the focus is on the syntactic complexity of the sentence, which varies in terms of masculine and feminine agent and patient roles, in differentiation between pronouns, and in different active and passive sentence structures (e.g., "the truck pulls the car"/"the car pulls the truck"; "the cat is bitten by the dog"/"the dog is bitten by the cat"). If the participant provides no answer after 5 s, a null score is given. More details about the test selection are not provided, so it is not clear whether they used all four modalities of these subtests of the BAT (hearing, speaking, writing, and listening). Nine patients in each group underwent four test sessions, one presurgery and then successively at 1, 6, and 12 months postsurgery. The statistical analyses were performed by direct group comparisons at each time point. One year after STN-DBS surgery, patients with PD performed better than the BMT group in qualitative language processing by showing lower error rates for comprehension of complex linguistic structures and syllabic fluency. No qualitative differences were found for morphological processing at any of the four time points. Furthermore, the STN-DBS group showed a significant increase in the total time required to execute the Stroop test after DBS as compared to the BMT control group, whereas error rates of the STN-DBS group dropped 1 year after DBS in comparison to 1 month after DBS. Altogether, the results were interpreted as a slowing of cognitive activity (as reflected in longer Stroop latencies and lower output in fluency tasks) but with an improvement in qualitative control of language production (fewer intrusion mistakes in the syllabic fluency task and fewer errors in the execution of the Stroop task). Moreover, the study shows that, after DBS, language function can temporarily be worsened but can recover or improve above baseline after some period.

The main focus of the study by Whelan et al. (2003) was on the theoretical role of the STN in language processing, and they used DBS in PD as a means to test this. This is the most "language-oriented" study of the 13 articles selected. Three extended language assessment batteries were administered, including five patients in the DBS group and 16 in the BMT group, measuring (a) "gross language" that included the BNT; (b) "high-level linguistics" tapping into lexical semantics by including the Word Test–Revised, the Test of Language Competence–Expanded Edition (Wiig & Secord, 1989), and animal and tool verbal fluency; and (c) "semantic processing" by using a semantic lexical decision task with words/nonwords and manipulations of number of meanings/meaning relatedness. Statistical analysis within the two PD groups and per individual language test indicated that the STN-DBS group showed longer response latencies in the lexical decision task 3 months after DBS surgery as compared to before surgery. There were no other significant differences for any of the language tests, including the BNT and verbal fluency, nor for the BMT control group. As the STN-DBS group only consisted of five patients, further analyses were performed by measuring RCIs per patient and per test, using clinically significant change relative to a normal control population. The RCI statistics did show a difference over time for the two PD groups on two (out of 20) language subtests, leading to a tentative conclusion that bilateral STN-DBS affects certain aspects of language functioning.

Discussion

The aim of this systematic review was to investigate the effect of bilateral STN-DBS on language function in

PD, with the strict selection criterion of a BMT control group. We found that the final selection of 13 studies included some form of verbal fluency task, and 12 of these originated from a broader neuropsychological test battery. This is by itself not surprising, given the fact that, in good clinical practice, verbal fluency is part of the standard neuropsychological test battery administered to exclude patients with PD suffering from dementia or other severe cognitive deficits from DBS (Troster, 2017). We also found that picture naming is the second most reported test (although not as frequently used as verbal fluency), again mostly originating from an extended neuropsychological test battery (the BNT). Furthermore, only two studies used other language tasks to investigate language function in PD after STN-DBS.

When reviewing the literature, we found that the more language-oriented studies used experimental designs in which on–off stimulation conditions were compared, thus after DBS surgery. These studies focused on stimulation effects instead of surgery effects. Moreover, these language studies compared the language performance of DBS patients with PD with a healthy control group, not suffering from PD, or without a control group at all. Thus, there is a clear paucity of data regarding performance of other language tasks than verbal fluency and picture naming.

So far, literature reviews have mainly focused on verbal fluency, rather than on picture naming, and in particular on semantic and phonemic fluency, as in the recent meta-analysis of Wyman-Chick (2016). We found three studies using other forms of fluency tests (e.g., alternating and syllabic fluency), all reporting a decline after DBS surgery. With respect to this most recent review on verbal fluency (Wyman-Chick, 2016), our inclusion of studies did not fully overlap with that review. First, we selected the Rothlind et al. (2015) study instead of the Weaver et al. (2009) study based on the same patient cohorts because it reported separate data for the STN target instead of combined STN and globus pallidus internus (GPi) data, and used RCIs. Second, we did not include the study of Ehlen et al. (2013) because it did not report the pre–post comparisons, but on–off stimulation comparisons. Finally, we identified six additional studies through our literature search, five from the reference lists of other studies (Demeter et al., 2017; Moretti et al., 2003; Morrison et al., 2004; Whelan et al., 2003; York et al., 2008) and one from the initial systematic search (Gironell et al., 2003).

We demonstrate that the general decline in verbal fluency is present for semantic and phonemic fluency (as reported earlier by Højlund et al., 2017; Wyman-Chick, 2016), but also for alternating and syllabic fluency. The decline could not be ascribed to disease progression, as we only included studies that had a matched PD control group (without surgery but on BMT). This control group did not show the same amount of decline.

With respect to picture naming, we found that it appears to be unaffected by DBS surgery in PD at the group level, in contrast to verbal fluency. Interestingly, individual change patterns (RCI) indicated that there was much more individual variability as to whether patients improved, remained stable, or declined after DBS for picture naming as compared to verbal fluency (Rinehardt et al., 2010; Whelan et al., 2003; York et al., 2008). After DBS, percentages of patients who declined on picture naming were 40%, 20%, and 23%, respectively, and improvement percentages were 5%, 40%, and 14%, showing large individual variability. For verbal fluency, by contrast, the results were more consistent: 15%, 30%, and 33% of patients declined, whereas 0%, 20%, and 3% of patients improved. Moreover, results from the study in our review using different follow-up times indicate that language function after DBS may improve at later points in time (Whelan et al., 2003).

In terms of underlying mechanisms, both verbal fluency and picture naming rely on word retrieval and language production. Furthermore, both involve more general cognitive processes and systems, such as initiation and semantic memory. The main difference is that the verbal fluency task stresses speed of processing, whereas picture naming assessed with the BNT does not—the score is based on errors in naming or failures to name. It is known that the BNT is suitable for identifying anomia in cases of stroke-induced aphasia, but more sensitive production tests tapping the speed of lexical retrieval could be more informative about language functioning (see, e.g., Brownsett et al., 2019; Moritz-Gasser et al., 2012; Shao et al., 2014).

The present review shows that, with respect to other language tasks, the two studies that did fulfill the selection criteria suffered from a lack of statistical power. They were both based on many different language tests and small group sizes. Furthermore, the statistical analyses were performed on direct group comparisons at each time point (Moretti et al., 2003) or were based on RCIs for only five STN-DBS patients (Whelan et al., 2003), making it difficult to draw general conclusions.

The present review did not investigate either the clinical relevance of reduced word fluency or its influence on quality of life. In a large study (105 STN-DBS patients), Smeding et al. (2011) found that patients reported improved quality of life after surgery despite a profile of cognitive decline with reduced verbal fluency. A similar pattern was found in the randomized controlled study of Weaver et al. (2009). STN-DBS patients gained a mean of 4.6 hr a day of on time without dyskinesia as compared with 0 hr a day for the BMT group and reported higher quality of life scores, despite decrements in cognitive processing. Reviews on risk–benefit reports of STN-DBS in PD are scarce (see Castrioto et al., 2014). In our clinical work, we experience that the reduction in verbal fluency should indeed be set off against the improvement in incapacitating and frustrating motor complications such as peak dose dyskinesias, prolonged off periods, or sudden off states. Theoretically, if reduction in verbal fluency with moderate effect sizes literally means that patients can produce a few words less per minute, whereas they improve on motoric outcome measures as frequently reported (Deuschl et al., 2006; Fasano et al., 2012; Weaver et al., 2009; Williams et al., 2010), then in this situation, the risk–benefit balance would favor DBS. Nowadays, there is general consensus that optimal medical care is provided by preselection of patients and by providing patients and caregivers with the best available information to make reasonable risk–benefit assessments per individual patient (see Castrioto, 2014; Troster, 2017, for useful recommendations).

An important limitation of our review is the fact that we did not find many studies using language tasks other than verbal fluency. Moreover, the number of studies examining picture naming is also relatively small. Therefore, strong conclusions cannot be drawn regarding a potential linguistic explanation for the general decline observed in verbal fluency in this population.

Conclusions and Future Directions

The present review shows the following: (a) In general, phonemic, semantic, and alternating fluency are negatively affected in patients with PD receiving STN-DBS as compared to BMT; (b) Picture naming, by contrast, appears unaffected; (c) There is a lack of studies including more language-oriented tasks other than verbal fluency or picture naming with a BMT control group and pre–post surgery comparisons in the literature; (d) There is large individual variability in post-DBS language performance; (e) RCIs are of clinical relevance for investigating differences in performance after DBS.

With respect to future research, previous reviews have pointed out that multicenter randomized controlled trials are needed with an STN-DBS group and a BMT control group, an on–off stimulation condition, and a pre–post surgery condition at different follow-up times. The results of the present review add to the recommendations that the investigation of language function in PD requires sensitive language tests with and without time pressure and that RCI statistics are useful in investigating individual differences in change in language function following DBS surgery.

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